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THE WESTERN Journal of Medicine

VOLUME 137 • NUMBER 1 JULY 1982

1 *Diagnostic Workup of Febrile Children Under 24 Months of Age: A Clinical Review*
MICHAEL SOMAN, MD

13 *Quality of Care in Women With Stage I Cervical Cancer*
JOSEPH CHU, MD, MPH; LINCOLN POLISSAR, PhD, and HISHAM K. TAMIMI, MD

18 *Infective Endocarditis Due to Anaerobic and Microaerophilic Bacteria*
FRANCISCO L. SAPICO, MD, and RADHA J. SARMA, MD

MEDICAL PROGRESS

24 *Calcium Channel Blockers* PRAKASH C. DEEDWANIA, MD

SPECIALTY CONFERENCE

32 *Turner's Syndrome*
Participants: JUDITH G. HALL, MD; VIRGINIA P. SYBERT, MD; ROGER A. WILLIAMSON, MD; NANCY L. FISHER, MD, and SUSAN D. REED, MS

MEDICAL STAFF CONFERENCE

45 *The Lowly Diphtheroid: Nondiphtheria Corynebacterial Infections in Humans*
Chief Discussant: RICHARD M. LOCKSLEY, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

53 *General and Family Practice—Epitomes of Progress*

EDITORIALS

60 *• Febrile Infants: A Commentary • Therapeutic Issues in Turner's Syndrome • Flawed Theories in a Real World • Calcium Channel Blockers and Cardiovascular Therapeutics*

CASE REPORTS

65 *CT Evidence of Subarachnoid Hemorrhage Due to Presumed Gnathostomiasis*
MICHAEL BRANT-ZAWADZKI, MD; CONSTANCE B. WOFSY, MD, and GISELA SCHECHTER, MD

67 *The Value of Artificial Beta Cell in the Management of Insulinoma*
LUBOMIR J. VALENTA, MD; HARVEY EISENBERG, MD; DON R. MILLER, MD; STERLING M. TANNER, MD; STEPHEN G. ROMANSKY, MD; ARTHUR H. RUBENSTEIN, MD; MARY MAKO; BRUCE F. CULLEN, MD; MICHAEL P. GOLDEN, MD, and ALAN N. ELIAS, MD

CORRESPONDENCE

76 *• Rising Health Care Costs • Another Indication for Coronary Bypass • Cheating Beyond Medical School • Bleeding After Liver Biopsy • Acute Arthritis in the Elderly • Pulmonary Embolism in Buerger's Disease • Traveler's Diarrhea • Birth Parents, Adoptive Parents and Adoptees • Western Student Medical Research Forum • Heparin-Induced Thrombocytopenia; With Reply by Author • On 'Opening Up' the Health Care System*

MEDICAL ETHICS

83 *Ethical Problems in Medical Practice—A Protocol for the Guidance of Physicians*
MALCOLM S. M. WATTS, MD; SISTER CORRINE BAYLEY, CSJ; FRANCIS A. HEALY, MD; WILLARD S. OSIBIN, MD; MINDY WERNER, BA, and LAURENS P. WHITE, MD

Detailed Table of Contents, See Advertising Pages 7 and 11

Books Received, See Advertising Page 29

Information for Authors, See May Issue, Advertising Page 60

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA: NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 16)**

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Because uropathogens on vaginal cells...

New *in vitro* studies indicate specific *E.coli* receptors on the urogenital epithelium may be an important factor in recurrent infection.

Researchers have recently identified a chemical receptor for *E. coli* on the uroepithelial cells of women who are subject to recurrent urinary tract infections.[1]

The receptor is a glycosphingolipid known as α-D-Gal*p* (1$\rightarrow$4)-β-D-Gal*p*. This carbohydrate is an antigen found on the red blood cells and the uroepithelial cells of women who have P-positive phenotypes.[1,2] It is *not* present on the erythrocytes or uroepithelial cells of women who are P-negative. Women who belong to the rare P-negative blood group had a much lower capacity for binding uropathogenic *E. coli* to their urogenital cells *in vitro* and had never experienced recurrent urinary tract infection. The cells from P-positive women, on the other hand, had a very high capacity for binding virulent *E. coli.* These women are generally much more likely to get recurrent infections. The chemical receptor appears to be a major factor responsible for this.[1]

Adherence of *E.coli* to vaginal mucosal cells increases susceptibility to urinary infections.

Another study, comparing women who experienced three or more urinary tract infections per year with healthy controls, found that vaginal cells from the women with recurrent urinary infections had a greater tendency to bind *E. coli in vitro*—even when the cells were cultured while there was no infection. The researchers speculated that deficient host defense mechanisms in vaginal mucosal cells may be responsible for recurrent urinary infections in many women.[3] *E. coli* and other uropathogens may colonize the vaginal introitus, adhere to receptors on mucosal cells and then infect the urinary tract.

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*Due to susceptible organisms such as *E. coli, Klebsiella-Enterobacter* and *Proteus* species.

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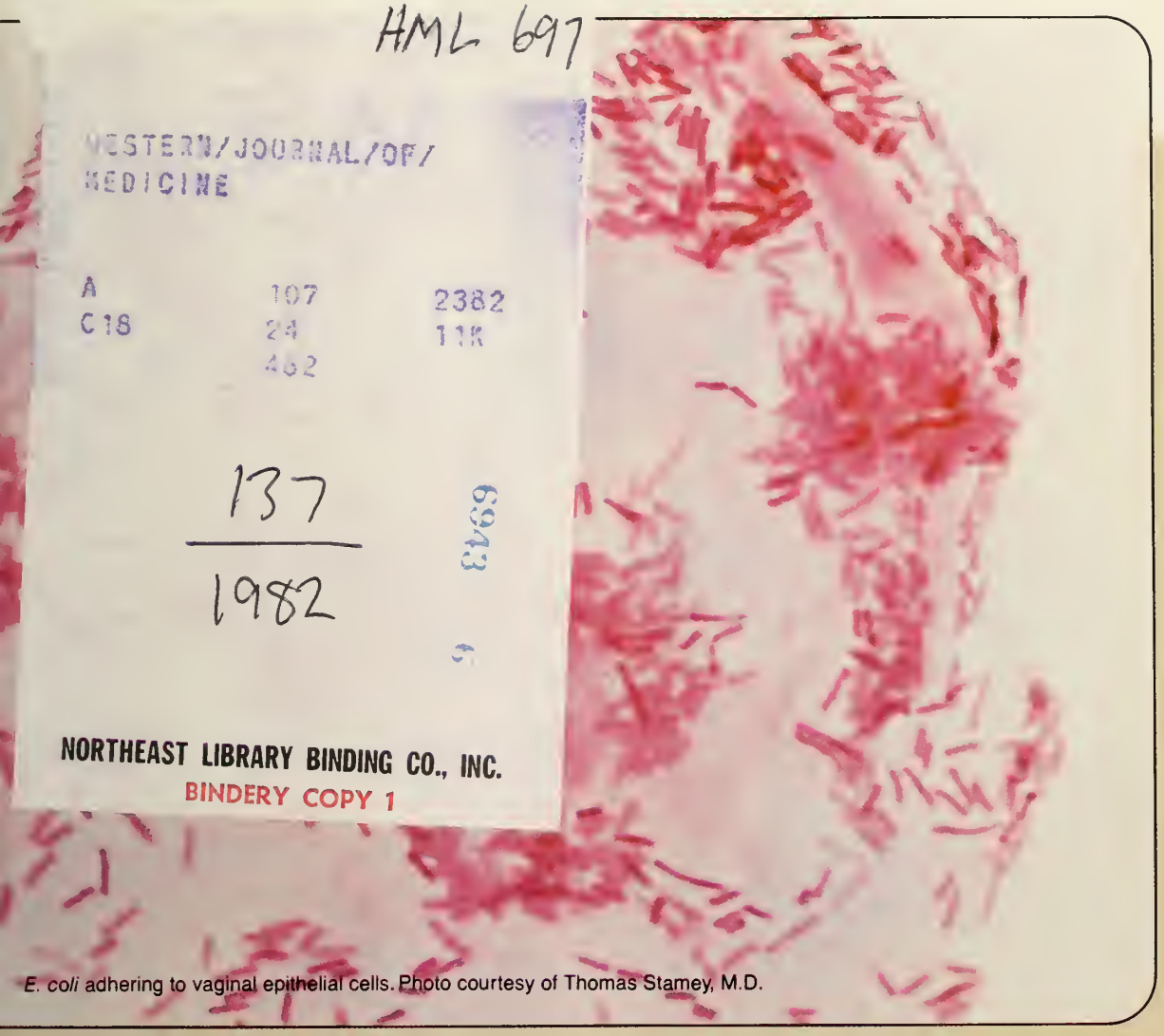

E. coli adhering to vaginal epithelial cells. Photo courtesy of Thomas Stamey, M.D.

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See next page for references and a summary of product information.

References: 1. Källenius G *et al: Lancet 2*:604-606, Sep 19, 1981. **2.** Lomberg H *et al: Lancet 1*:551-552, Mar 7, 1981. **3.** Schaeffer AJ *et al: N Engl J Med 304*:1062-1066, Apr 30, 1981. **4.** BacData Medical Information Systems: *Antibiotic Sensitivity Report*, Winter Series, 1981. **5.** Stamey TA, Condy M: *J Infect Dis 131*:261-266, Mar 1975. **6.** Rubin RH, Swartz MN: *N Engl J Med 303*:426-431, Aug 21, 1980.

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Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

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Dosage: Not recommended for infants less than two months of age.

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THE WESTERN
Journal of Medicine

VOLUME 137 • NUMBER 1 JULY 1982

TABLE OF CONTENTS

1 *Diagnostic Workup of Febrile Children Under 24 Months of Age: A Clinical Review*
MICHAEL SOMAN, MD
From the Department of Family Practice, University of California Davis Medical Center, Sacramento.

13 *Quality of Care in Women With Stage I Cervical Cancer*
JOSEPH CHU, MD, MPH; LINCOLN POLISSAR, PhD, and HISHAM K. TAMIMI, MD
From the Fred Hutchinson Cancer Research Center and the Departments of Epidemiology, Biostatistics and Obstetrics and Gynecology, University of Washington School of Medicine, Seattle.

18 *Infective Endocarditis Due to Anaerobic and Microaerophilic Bacteria*
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MEDICAL PROGRESS
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Chief Discussant: RICHARD M. LOCKSLEY, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

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Items of progress in general and family practice. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

53 *Gardnerella Vaginitis* JOSEPH E. SCHERGER, MD
54 *Better Management of Asthma With Mini-Wright Peak Flow Meter* DAVID N. KATZ, MD
55 *Advanced Trauma Life Support* RICHARD A. JOHNSON, MD
55 *Preoperative Preparation of Patients* WILLIAM C. FOWKES, MD
56 *Culdocentesis to Diagnose Ectopic Pregnancy and Pelvic Inflammatory Disease (PID)*
J. TIMOTHY MURPHY, MD
57 *Diethylstilbestrol (DES) Update 1982* T. WARNER HUDSON, MD, and JUSTINE McCABE, PhD
57 *Menstrual Extraction* MARTIN A. QUAN, MD
58 *Tetracycline for the Treatment of Gonococcal and Nongonococcal Urethritis*
HOWARD D. GROVEMAN, MD
58 *Sports Medicine—Objectives of the Preparticipation Evaluation*
JAMES C. PUFFER, MD

(Continued on Page 11)

Only one beta-blocker provides once-a-day round-the-clock protection in both angina pectoris and hypertension.

CORGARD®
[nadolol tablets]
IS THE ONE

Reliable 24-hour beta blockade at all titrated dosages

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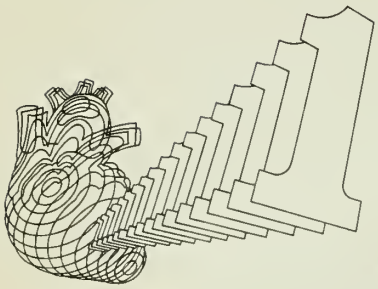
Innovators in cardiovascular medicine

See next page for brief summary.

The only once-a-day beta-blocker for both hypertension and angina pectoris



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets
DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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(Continued from Page 7)

EDITORIALS

60 *Febrile Infants: A Commentary* MOSES GROSSMAN, MD
From the Department of Pediatrics, San Francisco General Hospital Medical Center and University of California, San Francisco.

61 *Therapeutic Issues in Turner's Syndrome* FELIX A. CONTE, MD, and MELVIN M. GRUMBACH, MD
From the Department of Pediatrics, University of California, San Francisco.

62 *Flawed Theories in a Real World*

62 *Calcium Channel Blockers and Cardiovascular Therapeutics*
BRAMAH N. SINGH, MD, DPhil(Oxon), FRCP (Lond)
From the Department of Medicine, UCLA School of Medicine, and the Cardiology Section, Wadsworth Veterans Administration Medical Center, Los Angeles.

CASE REPORTS

65 *CT Evidence of Subarachnoid Hemorrhage Due to Presumed Gnathostomiasis*
MICHAEL BRANT-ZAWADZKI, MD; CONSTANCE B. WOFSY, MD, and GISELA SCHECHTER, MD
From the Departments of Radiology and Internal Medicine, University of California, San Francisco, and San Francisco General Hospital, and U.S. Public Health Service Hospital, San Francisco.

67 *The Value of Artificial Beta Cell in the Management of Insulinoma*
LUBOMIR J. VALENTA, MD; HARVEY EISENBERG, MD; DON R. MILLER, MD; STERLING M. TANNER, MD; STEPHEN G. ROMANSKY, MD; ARTHUR H. RUBENSTEIN, MD; MARY MAKO; BRUCE F. CULLEN, MD; MICHAEL P. GOLDEN, MD, and ALAN N. ELIAS, MD
From the Departments of Medicine, Radiology, Surgery, Pediatrics, Pathology and Anesthesiology, University of California, Irvine, California College of Medicine, and the Department of Medicine, University of Illinois College of Medicine, Chicago.

CORRESPONDENCE

76 *Rising Health Care Costs* ARTHUR H. COLEMAN, MD

76 *Another Indication for Coronary Bypass* ROBERT A. BRUCE, MD, and KENNETH F. HOSSACK, MD

77 *Cheating Beyond Medical School* ALAN L. LASNOVER, MD

77 *Bleeding After Liver Biopsy* PREETHAM KONDLAPOODI, MD

78 *Acute Arthritis in the Elderly* NEAL S. BIRNBAUM, MD

78 *Pulmonary Embolism in Buerger's Disease* GEORGE X. TRIMBLE, MD

79 *Traveler's Diarrhea* IVAN A. SHULMAN, MD

79 *Birth Parents, Adoptive Parents and Adoptees* JOSEPH H. DAVIS, MD

80 *Western Student Medical Research Forum* MICHAEL A. PATMAS, MD

Heparin-Induced Thrombocytopenia

80 ROBERT A. BAIRD, MD

81 SEBASTIAN CONTI, MD

81 KENNETH M. MOSER, MD, Reply

82 *On 'Opening Up' the Health Care System* GREGORY POLITO, MD

MEDICAL ETHICS

83 *Ethical Problems in Medical Practice—A Protocol for the Guidance of Physicians*
MALCOLM S. M. WATTS, MD; SISTER CORRINE BAYLEY, CSJ; FRANCIS A. HEALY, MD; WILLARD S. OSIBIN, MD; MINDY WERNER, BA, and LAURENS P. WHITE, MD
A Report of the Committee on Evolving Trends in Society Affecting Life, California Medical Association. The authors made up the Subcommittee on Ethics.

Books Received, See Advertising Page 29

Subscription Information, See Advertising Page 32

Information for Authors, See May Issue, Advertising Page 60

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO, OREGON, UTAH, WASHINGTON; WYOMING (See Advertising Page 16)

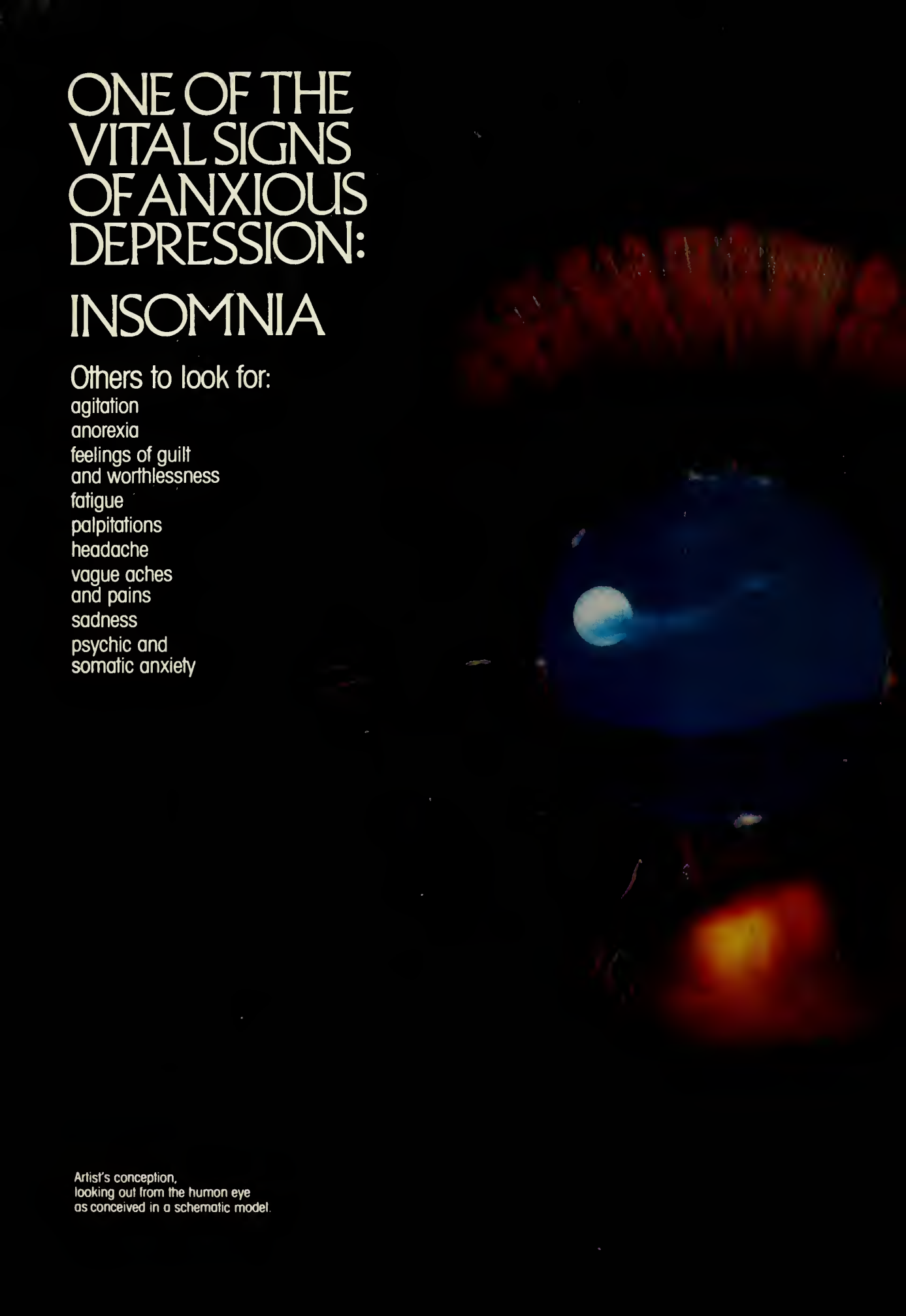
★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association and the Washington State Medical Association

ONE OF THE VITAL SIGNS OF ANXIOUS DEPRESSION:

INSOMNIA

Others to look for:

agitation
anorexia
feelings of guilt and worthlessness
fatigue
palpitations
headache
vague aches and pains
sadness
psychic and somatic anxiety



Artist's conception, looking out from the human eye as conceived in a schematic model.

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Limbitrol given once daily h.s. may be the best approach

Many patients respond readily to a single bedtime dose of Limbitrol, a convenient schedule that may enhance compliance and helps relieve the insomnia associated with anxious depression. Limbitrol also offers a choice of other regimens: t.i.d., or a divided dose with the larger portion h.s. In all cases, caution patients about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as driving or operating machinery.

in moderate depression and anxiety

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Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Specific therapy with h.s. dosage convenience

Please see summary of complete product information on following page.

LIMBITROL® TABLETS Tranquilizer—Antidepressant
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Relief of moderate to severe depression associated with moderate to severe anxiety
Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved Contraindicated during acute recovery phase following myocardial infarction
Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses Myocardial infarction and stroke reported with use of this class of drugs) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e g , operating machinery, driving)
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment Amitriptyline component may block action of guanethidine or similar antihypertensives Concomitant use with other psychotropic drugs has not been evaluated sedative effects may be additive Discontinue several days before surgery Limit concomitant administration of ECT to essential treatment See Warnings for precautions about pregnancy Limbitrol should not be taken during the nursing period Not recommended in children under 12 In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects
Adverse Reactions: Most frequently reported are those associated with either component alone drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs
Cardiovascular Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns
Anticholinergic Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus
Hematologic Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue
Endocrine Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels
Other Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling
Overdosage: Immediately hospitalize patient suspected of having taken an overdose Treatment is symptomatic and supportive I.V administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning See complete product information for manifestation and treatment
Dosage: Individualize according to symptom severity and patient response Reduce to smallest effective dosage when satisfactory response is obtained Larger portion of daily dose may be taken at bedtime Single *h s* dose may suffice for some patients Lower dosages are recommended for the elderly Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required Limbitrol 5-12 5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses
How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12 5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50

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July 16-17—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Saturday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

July 17-24—**Cardiovascular Medicine and Surgery: An Advanced Course.** STAN at Mauna Kea Beach Hotel, Kamuela. One week. 21 hrs. $325.

July 23-24—**Disaster Planning Symposium.** UCLA. Friday-Saturday.

July 23-25—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

July 24-25—**Vertigo '82.** Ear International at Hyatt Regency, Los Angeles. Saturday-Sunday. $200. Contact:: Ear International, 1245 Wilshire Blvd., Los Angeles 90017. (213) 481-2818.

July 24-30—**Laboratory Medicine.** USC at Marriott Hotel, Maui. One week. 27 hrs. $435.

July 25-29—**National Medical Association—87th Annual Convention and Scientific Assembly.** Hilton, San Francisco. Sunday-Thursday. 40 hrs. Contact: Christine Miller, Prog. Dir., NMA, 1301 Pennsylvania Ave., NW, Washington, DC 20001. (202) 347-8598.

August 5-6—**Advanced Fetal Heart Rate Monitoring.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Friday. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 6-8—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Clouds-Cal Neva Resort, Lake Tahoe. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 7-14—**Radiology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 27 hrs.

August 8-13—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 20 hrs. $300.

August 9-13—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Islandia Hyatt, San Diego. Monday-Friday. 33 hrs. $425.

August 11—**Back Pain.** LLU. Wednesday.

August 12-13—**National Institute for Care of the Elderly.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Thursday-Friday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 12-14—**Selection and Technique for Use of Muscle and Musculocutaneous Flaps in Reconstructive Surgery.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20 hrs. $420.

August 13-14—**Sports Medicine.** Univ. of Nevada-Reno School of Medicine at MGM Grand, Reno. Friday-Saturday. 12 hrs. Contact: Leanne Stone, Cont. Ed., Univ. of Nevada-Reno, Reno 89557. (702) 784-4046.

August 13-15—**Clinical Management of Coronary Disease and Exercise Testing.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 13-17—**Clinical Neuroanesthesia Workshop.** UCSD at Village Inn, La Jolla. Friday-Tuesday. 24 hrs. $325.

August 14-25—**25th Annual Postgraduate Refresher Course.** USC at Honolulu and Maui. 12 days. 37 hrs. $425.

August 14-25—**Update: Surgery 1982.** USC at Honolulu and Maui. 12 days. 35 hrs. $425.

August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

(Continued on Page 19)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Lo/Ovral Policy

A Policy of Extra-Low Dose Oral Contraception

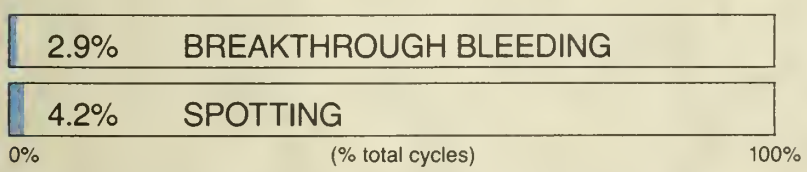
BENEFIT #1: EXTRA-LOW DOSE

The dosage is lower than "low." Lo/Ovral® contains an "extra-low" total hormone dose—30 mcg ethinyl estradiol and just 0.3 mg norgestrel. Even at this extra-low dose there was no reduction in contraceptive effectiveness. Nor any overall increase in breakthrough bleeding.*

BENEFIT #2: EARLY CYCLE BREAKTHROUGH PROTECTION

Lo/Ovral® offers your patients protection against breakthrough bleeding and spotting when they need it most—in the early cycles.* That's when they're usually most vulnerable to intermenstrual bleeding.

And in clinical trials totalling 22,489 cycles Lo/Ovral achieved a near-spotless record.* Just look below.



Cycle 1— 8.8%
Cycle 3— 3.3%

Cycle 1—10.6%
Cycle 3— 6.3%

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.

See full prescribing information.

SEE IMPORTANT INFORMATION ON FOLLOWING PAGE.

EXTRA-LOW DOSE LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

Oral contraceptive with a near-spotless record.

Wyeth Laboratories
Philadelphia, PA 19101

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IN BRIEF:

Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders 3. Cerebral-vascular or coronary-artery disease 4. Known or suspected carcinoma of the breast 5. Known or suspected estrogen-dependent neoplasia 6. Undiagnosed abnormal genital bleeding 7. Known or suspected pregnancy (see Warning No. 5) 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained sudden or gradual partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy: Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's, effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance fo carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

Wyeth Laboratories, Phila., Pa. 19101

Lo/Ovral Policy

A Policy of Extra-Low Dose Oral Contraception

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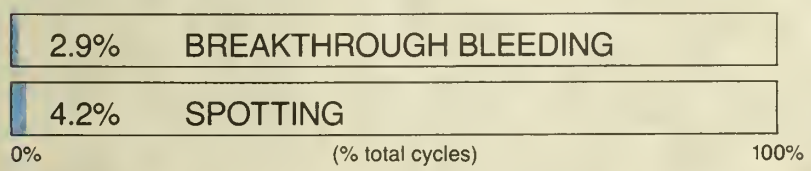

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yeth Laboratories
Philadelphia, PA 19101

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3 Cerebral-vascular or coronary-artery disease
4 Known or suspected carcinoma of the breast.
5 Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding 7 Known or suspected pregnancy (see Warning No. 5). 8 Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.
Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

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3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's Of cases found in women without predisposing risk factors (e g , irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC These are no longer marketed No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's Several studies have found no increase in breast cancer in women taking OC's or estrogens One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's
4 *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage This has been reported in short-term as well as long-term users Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock A few cases of hepatocellular carcinoma have been reported in women on OC's Relationship of these drugs to this type of malignancy is not known
5 *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy Male children so exposed may develop abnormalities of the urogenital tract Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy One case-control study estimated a 4 7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's Embryos with these anomalies are virtually always aborted spontaneously Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive Many clinicians recommend 3 months, although no precise information is available on which to base this The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy
6 *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use In one of the other studies, increased risk was apparent between 6 and 12 months' use
7 *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's For this reason, prediabetic and diabetic patients should be carefully observed while on OC's Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined
8 *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users
Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug
9 *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause
10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities
11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures
12 *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned
Precautions—GENERAL—1 A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests
As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.
2 Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size
3 Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related
4 OC's may cause some degree of fluid retention They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.
5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's If jaundice develops, OC's should be discontinued
6 Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.
7 OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency Clinical significance is undetermined
8 Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.
9 The pathologist should be advised of OC therapy when relevant specimens are submitted.
10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's:
a Increased sulfobromophthalein retention b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. c Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
d Decreased pregnanediol excretion. e Reduced response to metyrapone test
Information for the Patient—See Patient Package Labeling
Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline
Carcinogenesis—See Warnings on carcinogenic potential of OC's
Pregnancy—Category X See Contraindications, Warnings.
Nursing Mothers—See Warnings
Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.
The following adverse reactions have been reported in patients on OC's and are believed to be drug-related Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema, chloasma or melasma which may persist; breast changes: tendemess, enlargement, and secretion, change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses
The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria
Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females

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(Continued from Page 16)

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists at Stanford. Saturday-Sunday. 15 hrs. $275, members; $325, nonmembers. Contact: CSA, Ed. Prog. Div., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 21-22—**Office Orthopedics for the Internist and Family Practitioner.** UCLA. Saturday-Sunday. 12 hrs. $200.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session I.** UCSF at Golden Gateway Holiday Inn. San Francisco. 12 days. 80 hrs. $1,000.

August 26-28—**Advances in Diagnostic Imaging.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20½ hrs. $275.

August 29-September 3—**Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

August 30-September 1—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Napa Valley. Monday-Wednesday. 18 hrs. $275. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

August 30-September 4—**5th Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 38½ hrs. $595.

September 1—**Sports Medicine Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

September 7-17—**Intensive Residency in Occupational Medicine, III.** UCSF at Golden Gateway Holiday Inn, San Francisco. 11 days.

September 8—**Current Concepts in Menopausal and Post-Menopausal Care.** LLU. Wednesday.

September 11—**9th Annual Radiology Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Beverly Hilton, Beverly Hills. Saturday. Contact: Doris McMath, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 12-25—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

September 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 33 hrs. $425.

September 16-18—**4th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Thursday-Saturday.

September 20-22—**Alcoholism Treatment, Cooperation or Competition.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 20-24—**7th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Marriott, Maui. Monday-Friday. 21 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

September 21-22—**American Heart Association-Greater Los Angeles Affiliate—50th Anniversary Fall Symposium.** Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $70. Contact: Marilyn Cowan, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 24-25—**Antigens and Immunotherapy: Present and Future.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott, Newport Beach. Friday-Saturday. Contact: Warren Richards, MD, Allergy-Clinical Immunology Div., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054.

September 24-25—**Update in Internal Medicine—27th Annual Medical Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Century Plaza, Los Angeles. Friday-Saturday. Contact: Mark Anthony, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 24-25—**Sexual Issues in Medical Office Practice.** UCSF. Friday-Saturday. 10½ hrs. $125. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

September 24-26—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 25-26—**Thyroid Today—1982, A Clinical Update for the Practicing Physician, First Annual Symposium.** Cypress Foundation at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $130. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

September 25-October 3—**2nd Annual Recognition and Management of Diving Casualties.** UCSD at Sheraton Island Marina Inn, San Diego. 9 days. 60 hrs. Contact: Shirley Kolkey, Medicine, Education and Research Fndn., P.O. Box 81344, San Diego 92138.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: Registrar, ACEP, P.O. Box 61911, Dallas 75261. (214) 659-0911.

September 29-30—**39th Annual Brennemann Memorial Lectures.** L.A. Pediatric Soc. at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. $400. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

September 30-October 2—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

September 30-October 2—**Pulmonary Update.** UCSF. Thursday-Saturday.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Ctr., Torrance 90509. (213) 533-2233.

October 1-2—**Frontiers in Medicine: Implications for the Future.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. 16 hrs. $225.

October 1-2—**Intraocular Lens Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 1-2—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-7813.

October 1-3—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International

(Continued on Page 36)

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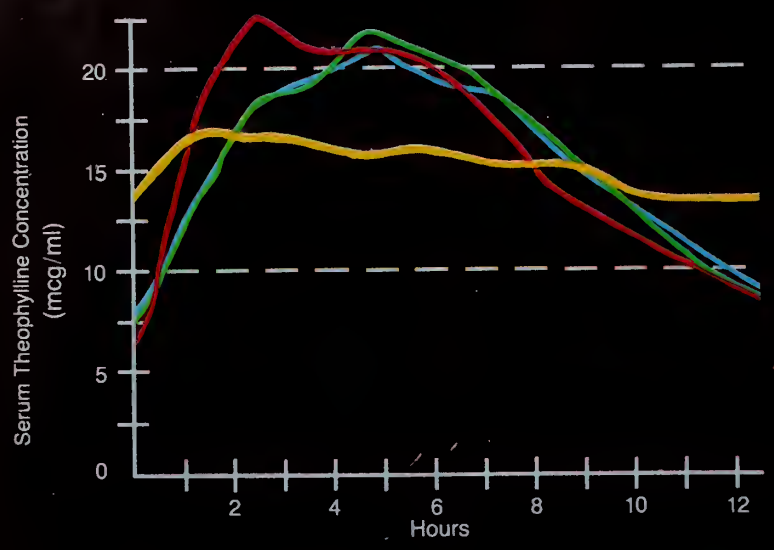

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†Adapted from Weinberger et al: J Pediatr 99 (no. 1): 145, July, 1981 Serum concentrations computer-projected from single dose absorption data in normal subjects supplied by the manufacturer or obtained experimentally (available on written request). Based on a rapid theophylline half-life of 3.7 hours, after achievement of steady-state levels with curves normalized to a concentration of 15 mcg/ml.

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(Continued on Page 44)

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PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:
—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply
—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand
—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page.

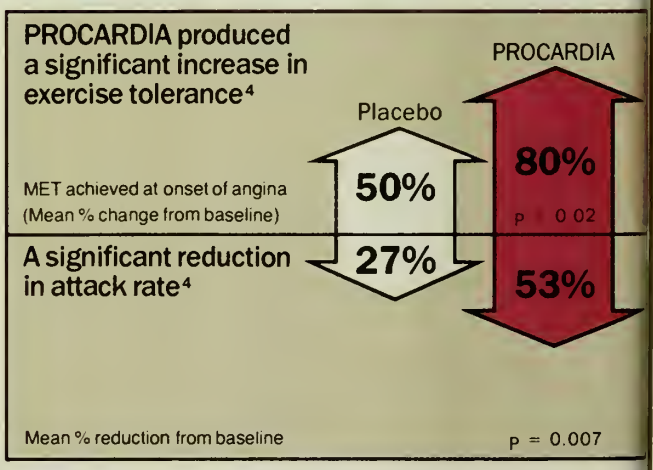
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy)



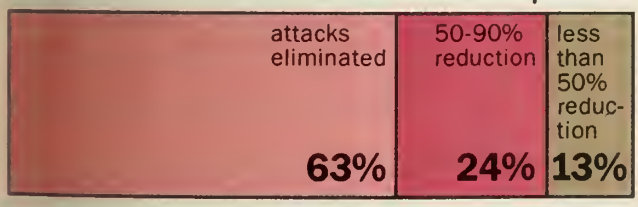
Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

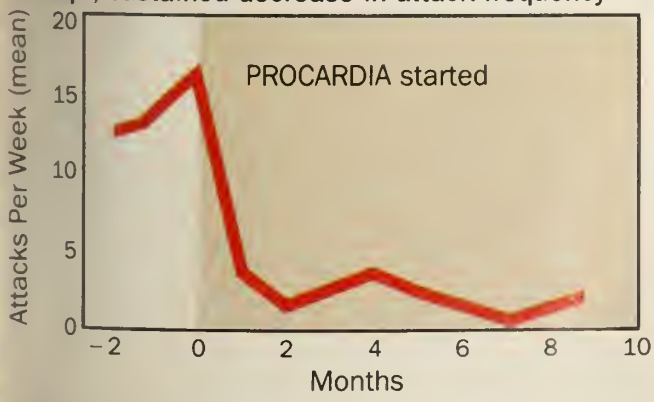
Please see PROCARDIA Brief Summary on last page

In vasospastic angina

PROCARDIA eliminated attacks in 63% of patients[5]

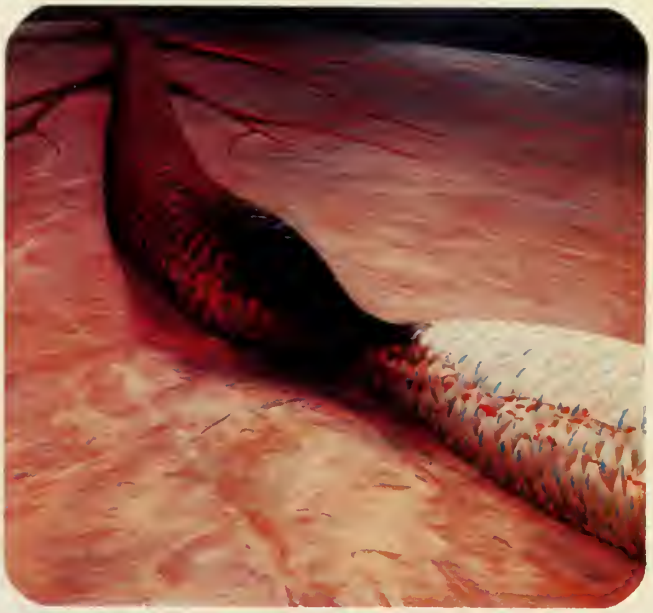


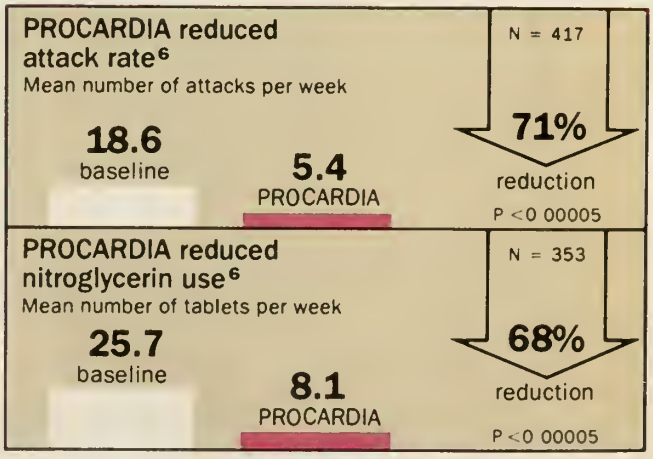
Prompt, sustained decrease in attack frequency[5]



Long-term, open study of 127 patients unresponsive to beta blockers and/or nitrates with symptoms of myocardial ischemia and demonstrated coronary artery spasm. PROCARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)





Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

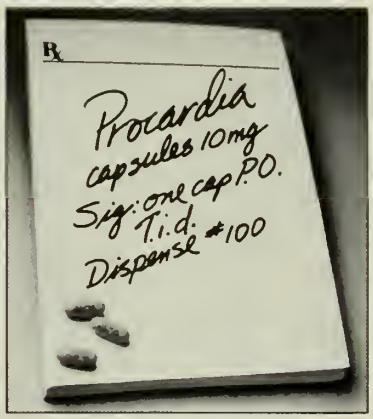
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d.*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose 180 mg/day.

References

1. Lichtlen PR, Engel H-J, Wolf R, et al. Regional myocardial blood flow in patients with coronary artery disease after nifedipine. In Lichtlen PR, Kimura E, Taira N (eds). *International Adalat® Panel Discussion. New Experimental and Clinical Results.* Tokyo: Excerpta Medica, 1978, pp 69–85.
2. Maseri A, Chierchia S. Angina pectoris—a new dimension, a new approach. Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E. *Introduction. New Concepts in Ischemic Heart Disease: The Role of Coronary Artery Spasm.* New York: Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645–657, October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator). Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, April 29, 1982.

PROCARDIA® CAPSULES For Oral Use
(nifedipine)
BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arteriel vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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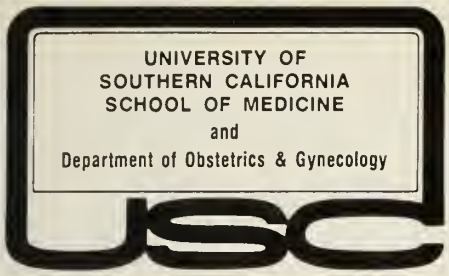

THE TWELFTH ANNUAL REVIEW COURSE IN GYNECOLOGY AND OBSTETRICS

This comprehensive course will be held at the Pasadena Hilton Hotel, Pasadena, California, Monday through Friday, October 11-15, 1982. It will review many basic concepts and update clinical management in every area of obstetrics and gynecology. Although the program will appeal to all, its direction will be toward those preparing for recertification examinations or the Oral OB/GYN Boards. A complete, well-organized syllabus covering the entire five-day program will be supplied each participant.

TUITION: $450 (includes 5 lunches)
CREDIT: 35 hours

Immediately following is the **REVIEW COURSE FOR GYNECOLOGIC PATHOLOGY,** scheduled for Saturday, October 16, 1982, also at the Pasadena Hilton. Review of pathological changes which occur in the female genital tract in response to inflammatory, neoplastic and abnormal hormonal stimuli as well as concepts of diagnosis and pathogenesis will be discussed; current terminology used in diagnosis will be emphasized. This course is designed primarily to assist those physicians who are preparing for the American Board of Obstetrics and Gynecology examinations.

TUITION: $75 (includes lunch)
CREDIT: 6 hours

PERINATAL MEDICINE

This comprehensive course will be held at the Royal Lahaina in Maui, Hawaii, February 5-11, 1983. The course will focus on current management approaches to solve clinical problems. The "Case Management Problems" will begin with the presentation of a difficult clinical case. Question and answer sessions will be emphasized.

TUITION: $425
CREDIT: 23 hours

Contact: **Associate Dean, USC School of Medicine, Postgraduate Div., 2025 Zonal Ave., Los Angeles, CA 90033; (213) 224-7051.**

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

COMPUTER APPLICATIONS FOR PATIENT CARE—Joseph D. Bronzino, PhD. Addison-Wesley Publishing Company, Inc., Medical/Nursing Division, 2725 Sand Hill Road, Menlo Park, CA 94025, 1982. 390 pages, $24.95 (hardcover).

GYNECOLOGIC ONCOLOGY—Fundamental Principles and Clinical Practice—Volumes 1 and 2—Edited by Malcolm Coppleson, MB, BS, MD(Syd) FRCOG, FRACOG, Churchill Livingstone, Inc., 19 West 44th Street, New York, NY 10036, 1981. 1,059 pages in 2 volumes, $187.50.

WHITMER'S GUIDE TO TOTAL WELLNESS—Visualization Techniques for a Better, Healthier, and Longer Life—R. William Whitmer. Doubleday & Company, Inc., 245 Park Ave., New York, NY 10017, 1982. 214 pages, $14.95.

WILLIS'S OXFORD CASEBOOK (1650-52)—Introduced and edited by Kenneth Dewhurst, TD, MD, DPhil, FRCPsych. Sandford Publications, Manor House, Sandford-on-Thames, Oxford OX4 4YN, England, 1981. 199 pages, price: 12 English Pounds, limited to 750 copies.

THE WOMANLY ART OF BREASTFEEDING, by La Leche League International. La Leche International, 9616 Minneapolis Avenue, Franklin Park, IL 60131, 1981, 368 pages, $12.95.

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Ativan®: (lorazepam) Agent of Change because...

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Unlike most benzodiazepines, Ativan has a short half-life, no active metabolites, and accumulation to steady state extends for only 2-3 days. Ativan is therefore less likely to cause excessive sedation.*

no interaction with drugs metabolized by P450 enzymes

Because it is metabolized by simple conjugation rather than complex oxidative reactions, Ativan does not compete with other drugs for hepatic P450 microsomal enzymes. Concomitant use with Tagamet® (cimetidine), for example, does not result in delayed clearance or increased sedation†—effects which have been reported with other benzodiazepines.[1-5]

greater control of therapy

The short half-life of Ativan facilitates more rapid response to dosage adjustments, aiding you in titrating therapy to the patient's changing needs. Once you decide to discontinue Ativan, it will be out of your patient's system 4 days after the final dose—unlike the long-acting, multi-metabolite benzodiazepines which take as long as 2 weeks to be totally eliminated.

Wyeth Laboratories
Philadelphia, PA 19101

References:
1. Klotz U, Reimann I: N Engl J Med 302:1012-1014, 1980.
2. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med 93:266-268, 1980.
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology 79:912-916, 1980.
4. Sellers EM, Naranjo CA, Peachey JE: N Engl J Med 305:1255-1262, 1981.
5. Ruffalo RL, Thompson JF, Segal JL: South Med J 74:1075-1078, 1981.

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*Pharmacokinetics cannot as yet be directly related to efficacy.
†All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol.

See important information on following page.

Ativan® for Anxiety (lorazepam) IV

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating) Addiction-prone individuals, e.g drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study No studies regarding mutagenesis have been performed

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4 2%) and unsteadiness (3.4%) Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P Usefulness of dialysis has not been determined

Ativan®
for (lorazepam)
Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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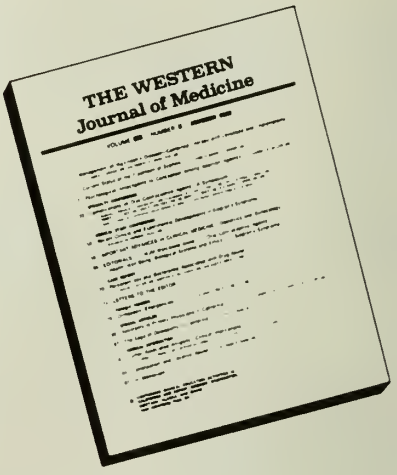

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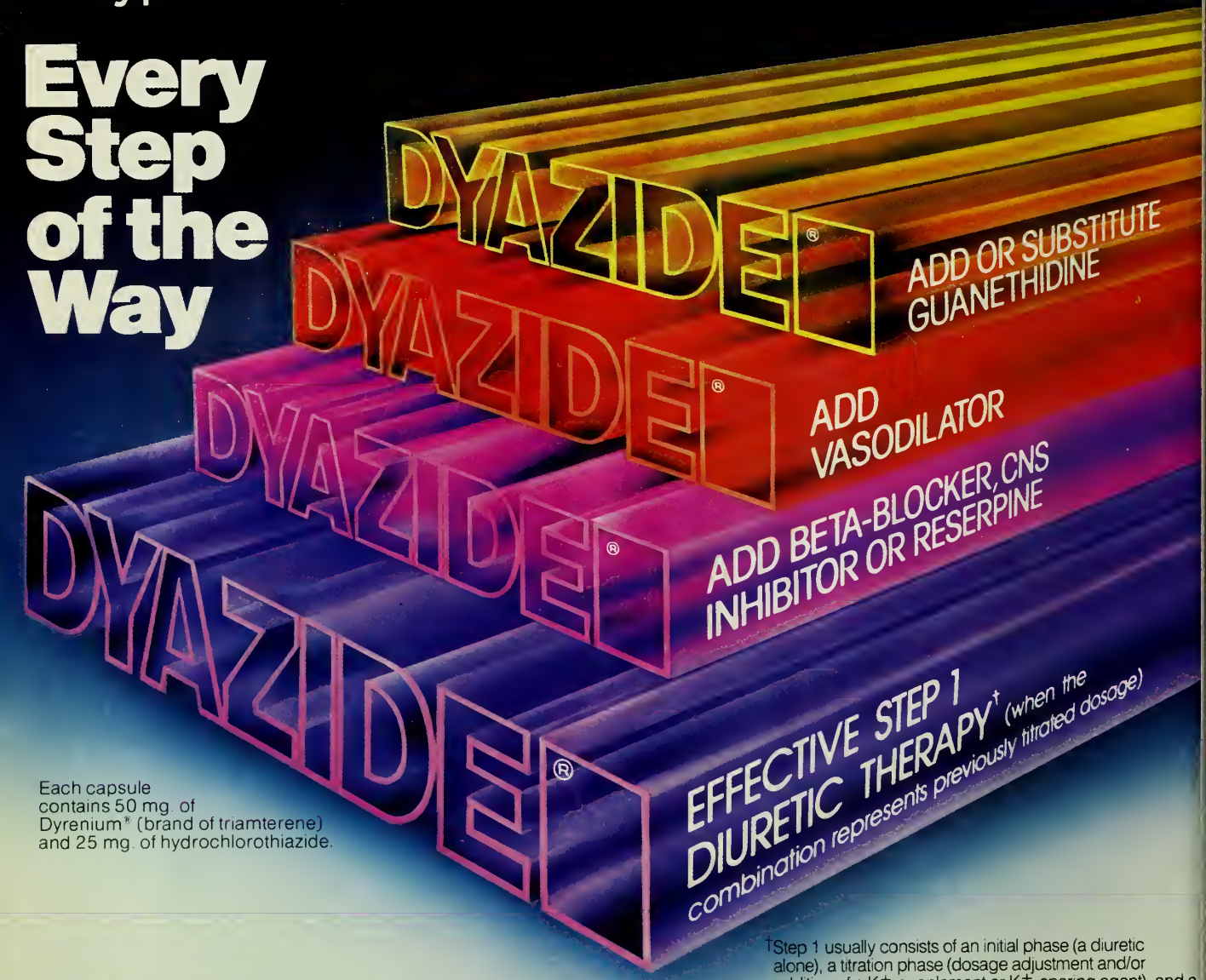

Each capsule contains 50 mg. of Dyrenium* (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

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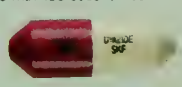

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Refer to: Chu J, Polissar L, Tamimi HK: Quality of care in women with stage I cervical cancer. West J Med 1982 Jul; 137:13-17

Quality of Care in Women With Stage I Cervical Cancer

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A study was done to assess the quality of care received by women with stage I cervical cancer. Through a population-based registry serving 13 counties of western Washington, including Seattle, we identified all women residents in whom local-stage cervical cancer developed between January 1974 and December 1978 (N=369). The cases were subdivided into stage IA (microinvasive) and stage IB (frankly invasive). Quality of care was defined as optimal or suboptimal at the outset of the study; this definition applied to all cases. In patients with stage IB cervical cancer, striking relationships were found between the quality of care and initial and referral hospital characteristics and physician's specialty. No differences were found, however, in three-year survival between the optimally and suboptimally treated groups.

THE PURPOSE OF THIS STUDY was to assess the quality of care received by women with stage I cervical cancer and to explore the relationship between quality of care and hospital, physician and patient-related variables. Investigating the process of care, that is, how medical resources are used in the treatment of patients, is useful in assessing the quality of care. Although this approach does not measure final outcome, it does indicate the extent to which physicians follow medical standards.

Methods

With the assistance of the Cancer Surveillance System (CSS) a population-based tumor registry serving 13 counties of western Washington, including Seattle, all women residents newly diagnosed with stage I cervical cancer from January 1, 1974, to December 31, 1978, were identified. In all, 156 women had stage IA (microinvasive) and 213 women stage IB (frankly invasive) disease. Abstracts of the medical records of all the women were reviewed for accuracy of substaging and were reclassified (5 percent) as necessary. Patient characteristics, tumor histology, characteristics of county of residence (urban or rural and the presence of a radiation facility), physician characteristics and initial and referral hospital characteristics were obtained.

We defined quality of care received and coded it (J.C.) as a dichotomous variable (optimal or suboptimal). Optimal care in stage IA was defined as having a cone biopsy for diagnosis followed by a simple hysterectomy for treatment.[1,2] Optimal care in stage IB was defined as a biopsy for diagnosis with definitive treatment by radical hysterectomy and lymph node dissection, radiation followed by simple hysterectomy or primary

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Submitted February 16, 1982.

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ABBREVIATIONS USED IN TEXT

ACOS = American College of Surgeons
CSS = Cancer Surveillance System

radiation.[3,4] Women treated with primary radiation for stage IB cervical cancer were classified as receiving optimal care if treated with external or intracavitary or both forms of radiation. Information concerning the number of rads received or radiation fields was incomplete and was not taken into account in the classification of the quality of care. We were also unable to determine whether patients refused optimal care, for example, to avoid travel to an out-of-area hospital.

The patient characteristics of age, race and marital status were routinely coded by the CSS. The educational level (percentage of high school graduates among persons aged 25 or older in the patients' census tract) was used as the index of socioeconomic status. This variable was available only for the three urban counties (King, Pierce and Snohomish) in which 68 percent of the patients resided. Tumor histology (squamous or adenocarcinoma) was coded from the CSS abstract forms. Physician characteristics (age and specialty) were obtained through a Washington State physician survey completed in 1979; these characteristics were obtained for all physicians whose patients were designated as receiving suboptimal care and for physicians of a 50 percent random sample of patients who were designated as receiving optimal care, for a total of 184 patients. Hospital characteristics included (1) the number of new cancer patients per year (obtained from the CSS), (2) whether the hospital had an American College of Surgeons (ACOS) approved cancer program (ascertained from the Bulletin of the American College of Surgeons)[5] and (3) the hospital's peer group (determined by the Washington State Hospital Commission, which uses a variety of criteria, such as the presence or absence of a house-staff training program and the types of services provided; 1 = lowest, 5 = highest).[6] When multiple hospitals were listed, the hospital with the highest peer group was designated as the referral hospital. When only one hospital was given, it was considered both the initial and the referral hospital.

The data were cross-tabulated with quality of care as the dependent variable and other characteristics as independent variables. Patients with stages IA and IB cervical cancer were tabulated separately and chi-square was used as a test of independence. Multiple regression was used to determine the relative importance of factors related to optimal care. Survival curves were computed for optimal and suboptimal groups in stages IA and IB. Survival times were censored depending on the date of last follow-up.

Results

Approximately 14 percent of women with stage IA disease (22/156) and 15 percent of women with stage IB disease (32/213) received suboptimal care. In the overwhelming majority of patients who received suboptimal care errors were made in diagnosis rather than in therapy—85 percent of suboptimal cases in stage IA and 72 percent of suboptimal cases in stage IB.

Patient Characteristics

Of the four demographic factors (age, race, marital status and educational level) examined in stages IA and IB cervical cancer, none were statistically significant (at $P = .05$) in relation to suboptimal care. But several factors showed interesting trends. A lower percentage of nonwhites with stage IA disease received optimal care than whites (nonwhites: 60 percent optimal out of 10 cases, compared with whites: 85 percent out of 142 cases, $P = .10$). Also, among women with stage IA disease, there was a trend toward more receiving optimal care as the percentage of high school graduates in the census tract increased (low education level tracts: 72 percent optimal care; medium education level: 81 percent; high education level: 96 percent; $P = .06$). Neither of these demographic relationships was seen in stage IB disease.

Tumor Characteristics

Patients with squamous cell carcinoma received a similar proportion of optimal care as patients with adenocarcinoma of the cervix.

County of Residence

A higher percentage of women who were residents of rural counties (90 percent) received optimal care than residents of urban counties (82 percent). Similarly, patients who resided in counties without radiation facilities were more likely to receive optimal care than patients in counties with radiation facilities (92 percent vs 81 percent). Although these relationships were

not statistically significant, they were consistent in both stages IA and IB. Women with stage IB cervical cancer were more likely to receive optimal care if they did not have all their hospital care in their home county (home county only: 76 percent optimal vs some hospital care outside county: 94 percent, $P=.006$). This analysis excluded residents of King County, which is the major referral center, and virtually all residents of King County receive care in-county. Women with stage IB cervical cancer who received suboptimal care were more likely to have been admitted to only one institution (see Table 1).

Initial and Referral Hospital Characteristics

The quality of care received by women with stage IB disease was related to the number of new cancer patients seen per year and the peer group of the initial and referral hospital (see Table 1). There was also a strong relationship between quality of care and ACOS approval for the referral hospital in the stage IB cases. Interestingly, no hospital characteristics of stage IA cases were related to the quality of care.

TABLE 1.—*Selected Hospital Characteristics in Relation to Optimal Care Received by Women With Stage IB Cervical Cancer (N=213)*

Item/Categories		*Number of Patients in Category*	*Percentage That Received Optimal Care*	*P(x²)*
Number of hospitals entered				
1		117	79	
2 or more		96	93	.02
Number of new cancer patients/year*				
Initial hospital:	0-199	56	79	
	200-499	60	82	
	500+	97	91	.09
Referral hospital:	0-199	19	47	
	200-499	36	81	
	500+	158	91	<.0001
Peer group†				
Initial hospital:	1-3	113	81	
	4-5	100	90	.08
Referral hospital:	1-3	12	67	
	4-5	201	87	.001

*Obtained from the Cancer Surveillance System.

†Determined by the Washington State Hospital Commission using a variety of criteria; 1=lowest, 5=highest number of criteria met.[6]

TABLE 2.—*Optimal Care Received by Women With Cervical Cancer in Relation to Physician Specialty*

Stage	*Item/Categories*	*Number in Category*	*Optimal Care (percent)*	*P(x²)*
	Physician specialty			
IA	Obstetrics and gynecology	78	78	
	Family and general practice	16	63	
	General surgery	6	67	.44
IB	Obstetrics and gynecology	71	80	
	Family and general practice	21	67	
	General surgery	12	17	<.00005

Physician Characteristics

Physicians specializing in obstetrics and gynecology provided a higher proportion of optimal care for women with stage IA disease than did those specializing in general surgery or family and general medicine. This relationship was even stronger in women with IB disease (see Table 2). There were no differences in age of physicians for those women who received optimal and suboptimal care.

Physicians doing radical surgical procedures were examined as a subgroup to document the number of such procedures each performed a year as an indicator of experience. Thirteen physicians had carried out at least one radical hysterectomy and lymph node dissection during the five-year study period. However, only five of the physicians had performed more than one radical procedure during the five-year period.

Survival

We found no significant difference in the three-year survival rate between optimal and suboptimal groups in stage IA (95 percent) or stage IB (89 percent) cervical cancer.

Multivariate Analysis

Because referral hospital characteristics and physician specialty were both strongly related to optimal care, we carried out a multiple regression analysis to determine which set of factors was more predictive of optimal care. Only the 184 patients for whom we coded physician specialty were included. Because optimal care was dichotomous and did not satisfy the assumption of a normally distributed dependent variable, we considered only the proportion of variance explained by each set of factors and did not consider statistical significance. For stages IA and IB cases the physician specialty explained more of the variation in optimal care than the hospital factors, regardless of the order of entry of each set of factors into the regression model. Both sets of factors combined explained 26 percent of the variation in optimal care among stage IB

cases but only 3 percent of the variation among stage IA cases.

Comment

Two factors could have potentially impaired our ability to determine the relationship between quality of care and other variables. First, there is a potential bias in a single reviewer determining the quality of care, even though the treatment of stage IA and IB cervical cancer is well established in the literature.[1-4] To assess this bias 41 case abstracts were randomly selected and independently reviewed by a second physician (H.K.T.), who agreed on the optimal-suboptimal assignment in 39 of the 41 cases. Kappa, a statistic that measures the agreement between two rates not due to chance,[7] was 0.90 ($P<.0001$). Thus, the classification of cases as optimal or suboptimal appears to be highly reproducible.

A second potentially limiting factor is an error in the pathologic and treatment data collected on the abstract forms. We were not able to review the pathologic slides in this study. This slide review would be particularly important in establishing a diagnosis of microinvasive or stage IA cancer. In a few instances where the medical record abstract indicated the depth of penetration, the case was reclassified from invasive to microinvasive disease or vice versa (5 percent of cases). Otherwise, the pathologist's diagnosis was accepted. Errors in collecting treatment data are unlikely. A radical operation, simple hysterectomy or cone biopsy probably would not be overlooked because they would be recorded in several different places in a medical chart. It is also unlikely that radiation procedures would be missed because they would be indicated in the medical records if done in hospital or in radiologists' private offices, where the CSS sends abstractors to review records.

We had hypothesized that women with stage IB cervical cancer were more likely to receive optimal care if it was not all given in the home county (excluding King County, which is a referral center). This hypothesis was supported by the data. The reason is partially due to the surgical expertise in the larger hospitals of the referral counties. The relationship of suboptimal care and hospital care at a single institution is the result of less patient referral to larger centers. The expertise of the larger centers is shown by the positive relationships between optimal care and hospital characteristics (number of new cancer patients per year, peer group and ACOS approval). These findings are consistent with those of Luft and associates,[8] who found an inverse relationship between institutional surgical volume and mortality.

Physicians specializing in obstetrics and gynecology provided a higher frequency of optimal care than physicians in general practice or family practice and in general surgery, especially for stage IB patients. This finding is perhaps not surprising because those formally trained in obstetrics and gynecology should be most cognizant of the best methods of diagnosing and treating cervical cancer. Payne and Lyons,[9] in a study of quality of care in Hawaii, also found that physicians trained in obstetrics and gynecology performed better than other physicians in the care of cervical cancer patients, as measured by a physician performance index.

The lack of difference in the three-year survival rates between the optimal and suboptimal care groups in stage IA cervical cancer is not surprising because most of the patients classified as suboptimal underwent simple hysterectomy for suspected carcinoma in situ and were diagnosed as having microinvasive cervical cancer from the pathologic specimen. So, even though patients did not have an optimal diagnosis, they did finally receive the standard definitive treatment. There was also no significant difference in survival rates between the optimal and suboptimal groups in stage IB. This lack of difference was probably due either to the short follow-up time or the possible efficacy of radiation immediately after simple hysterectomy, or both.[10,11]

It should be noted that 22 women with stage IB cervical cancer in the suboptimal group received simple hysterectomy followed by radiation. Although we had no method of assessing morbidity for these cases, this dual type of therapy does increase the risk of complications and financial cost.

Summary

Evidently admission to hospitals with expertise in cancer care and diagnosis and treatment by an obstetrician-gynecologist promote optimal care. These findings suggest that (1) additional education on the diagnosis and treatment of cervical cancer should be offered to physicians who may encounter such cases in practice and (2) an approach to cervical cancer care organized by geographic region should be encouraged.

Due to the limitations of the medical records

review approach used here, a study based on patient and physician interviews should be carried out to determine the decision-making process that led to both optimal and suboptimal care.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Speech Perception With Hearing Aids and Cochlear Implants

Owens E, Telleen CC

Archives of Otolaryngology
1981 Mar; 107:160-163

DISCIPLINES: General Medicine, Otolaryngology

READABILITY: Very good

Excellent presentation of well-documented material, easily understood. Particularly suited for specialists in audiology and speech, and hearing communication specialists.

—ROGER BOLES, MD
San Francisco

Interferon Therapy in Juvenile Laryngeal Papillomatosis

Haglund S, Lundquist P-G, Cantell K, et al

Archives of Otolaryngology
1981 Jun; 107:327-332

DISCIPLINES: Pediatrics, Pulmonary Medicine, Thoracic Surgery, Otolaryngology

READABILITY: Very good

Important clinical experimental studies.

—ROGER BOLES, MD
San Francisco

Placebo Effect in Surgery for Meniere's Disease—A Double-blind, Placebo-Controlled Study on Endolymphatic Sac Shunt Surgery

Thomsen J, Bretlau P, Tos M, et al

Archives of Otolaryngology
1981 May; 107:271-277

DISCIPLINES: General interest, especially Neurology

READABILITY: Very good

Long-standing troublesome problems. These clinical research data have been highly acclaimed by otolaryngologists.

—ROGER BOLES, MD
San Francisco

Refer to: Sapico FL, Sarma RJ: Infective endocarditis due to anaerobic and microaerophilic bacteria. West J Med 1982 Jul; 137:18-23

Infective Endocarditis Due to Anaerobic and Microaerophilic Bacteria

FRANCISCO L. SAPICO, MD, *Downey, California, and* RADHA J. SARMA, MD, *Los Angeles*

Seven cases of infective endocarditis (IE) due to anaerobic or microaerophilic bacteria were seen in a period of 42 months at Rancho Los Amigos Hospital (Downey, California), representing 10.6 percent of the total number of 66 cases that carried the diagnosis of IE. Five of the 66 patients had polymicrobial endocarditis. Three of five patients with polymicrobial endocarditis had at least one anaerobic or microaerophilic microorganism isolated from the blood, and all five patients practiced intravenous drug abuse. Six of the seven patients with anaerobic or microaerophilic IE were women. The three patients who had anaerobic Gram-negative bacillary endocarditis were drug abusers. None of the isolated organisms were Bacteroides fragilis. *The following heart valves were involved in the seven patients with anaerobic or microaerophilic IE: tricuspid (three), mitral (two), aortic (one) and tricuspid plus aortic (one). Three of the seven patients had preexistent valvular disease, and two required tricuspid valvulectomy. Only one patient had serious systemic embolism (cerebral), but all four drug abusers had septic pulmonary embolism. All seven patients recovered with appropriate antimicrobial therapy.*

INFECTIVE ENDOCARDITIS (IE) due to anaerobic and microaerophilic microorganisms has been considered a relatively uncommon condition. In 1970 Felner and Dowell[1] from the Centers for Disease Control reviewed anaerobic bacterial endocarditis and reported an incidence of 1.3 percent from the literature. In 1977 Pelletier and Petersdorf[2] reviewed 125 cases of IE seen at the University of Washington Hospitals and reported three cases of endocarditis due to microaerophilic streptococci and five cases due to strict anaerobes (6.4 percent of total). Their review showed a 9.6 percent incidence of cases with negative cultures. More recently von Reyn and co-workers[3] reported a 7.7 percent incidence of anaerobic or microaerophilic IE in 123 total cases, with a 5.5 percent incidence of cases with negative cultures.

At Rancho Los Amigos Hospital, we have recently seen seven cases of IE due to anaerobic or microaerophilic bacteria. We have reviewed the clinical characteristics of this disease in these seven patients to gain a clearer understanding of the clinical features associated with it. We have also reviewed our experience with infective endocarditis to determine whether the incidence of endocarditis

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Submitted, revised, December 14, 1981.

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ABBREVIATIONS USED IN TEXT

IE = infective endocarditis
TSB = trypticase soy broth

due to these particular microorganisms differs from that observed by others.

Patients and Methods

A list of patients discharged from January 1977 to June 1980 with a diagnosis of infective endocarditis was obtained from the medical records department of the Rancho Los Amigos Hospital. Criteria used for establishing the diagnosis of IE were as previously described.[3] To be included in the general survey, patients had to meet the minimal criteria set for the diagnosis of "possible endocarditis." The charts were reviewed for general patient data and to determine which patients had IE due to anaerobic or microaerophilic bacteria. These latter charts were then analyzed in detail and various clinical characteristics were tabulated and evaluated retrospectively. The patients included in this study were seen by one or both of the authors during their admission for IE.

In our hospital the usual procedure for doing blood cultures was to inject 10 ml of blood into each of a two-bottle set of broth culture media. One bottle contained 9 ml of trypticase soy broth (TSB, Clinical Standards, Carson, Calif.) and the other 90 ml of thioglycolate broth (Thio, Clinical Standards). Each of these bottles contained 0.025 percent of sodium polyanethol sulfonate (SPS). Inoculated bottles of TSB were immediately vented by aseptically inserting sterile, cotton-plugged airway needles. Broth bottles were incubated at 35°C for at least seven days. Aliquot specimens from the bottles were taken for subculture on the first, third and fifth day if no growth was seen. Microbiologic isolation and identification were carried out by conventional methods.[4-6]

Results

From January 1977 to June 1980 66 patients were discharged from Rancho Los Amigos Hospital with a diagnosis of infective endocarditis. Of these 66, there were 39 men and 27 women. In 4 of the 66 patients the diagnosis of IE was made from clinical features consistent with the disease but their blood cultures were consistently negative (6.1 percent of total). Of the 66 patients, 44 were intravenous drug abusers (66.6 percent). Seven patients (10.6 percent) had anaerobic or microaerophilic endocarditis. Table 1 shows the microorganisms isolated from blood cultures in the 62 patients with positive cultures. Of the ten anaerobic and microaerophilic isolates, seven organisms were isolated from four drug abusers and three were isolated from three who did not use drugs. All seven patients with anaerobic or microaerophilic IE showed features of at least "probable" endocarditis.[3] Anaerobes and microaerophiles composed 14.3 percent of the total number of isolates from drug abusers and 15.0 percent of the total number of isolates from non-drug-abusers. It should also be noted that all five of the anaerobic Gram-negative bacilli were isolated from three intravenous drug abusers and that none of the cultures from the nonaddicted patients yielded these organisms. One of the anaerobic Gram-negative bacilli isolated was reported to be an "anaerobic *Eikenella corrodens*," which would not grow aerobically or in 5 percent carbon dioxide (CO_2). The exact biochemical profile of this organism could not be elucidated, but there is a possibility that it could have been *Bacteroides corrodens*.

Table 2 summarizes the clinical features of our seven patients with anaerobic or microaerophilic

TABLE 1.—*Blood Culture Isolates From 62 Patients With Infective Endocarditis at Rancho Los Amigos Hospital, January 1977 to June 1980*

Microorganisms Isolated	*Patient Classification*	
	Drug Abuser	*Non-drug Abuser*
Aerobes		
Staphylococcus aureus	27	3
Viridans *Streptococcus* (α-hemolytic)	9	8
Group A *Streptococcus*	2	1
Pseudomonas aeruginosa	1	0
Enterobacter sp	1	0
Hemophilus aphrophilus	1	0
Streptococcus pneumoniae	0	1
Pasteurella multocida	0	1
Eschericlia coli	0	1
Staphylococcus epidermidis	0	1
Eikenella corrodens	1	0
Candida albicans	0	1
TOTAL	42	17
Anaerobic or Microaerophilic Organisms		
Microaerophilic *Streptococcus*	2	2
Peptostreptococcus	0	1
Bacteroides melaninogenicus	1	0
"Anaerobic *Eikenella corrodens*"	1	0
Bacteroides sp	1	0
Fusobacterium nucleatum	1	0
Fusobacterium sp	1	0
TOTAL	7	3

TABLE 2.—*Clinical Characteristics of 7 Patients With Anaerobic and Microaerophilic Endocarditis at Rancho Los Amigos Hospital, January 1977 to June 1980*

Patient No.	*Age*	*Sex*	*Intravenous (IV) Drug Abuse (Duration)*	*Valve(s) Involved*	*Echocardiogram Positive**	*Cardiac Murmur*	*Probable Source of Infection*	*Complications*	*Blood Culture Isolates*	*Antibiotic Therapy*	*Outcome*
1	22	♀	Methylphenidate hydrochloride, heroin, barbiturates (5 yrs)	Tricuspid	Yes	Yes	IV drug abuse	Septic pulmonary embolism with cavitation	*Staphylococcus aureus*, microaerophilic *Streptococcus, Enterobacter cloacae*	Methicillin sodium given IV + gentamicin sulfate + penicillin × 10 wks	Tricuspid valvulectomy. Discharged asymptomatic
2	50	♀	None	Mitral (RHD)	No	Yes	?	Cerebral embolus	*Peptostreptococcus* sp	Penicillin G given IV × 5 wks; SM given IM × 1 wk	Discharged asymptomatic
3	38	♀	Heroin ("many years")	Porcine tricuspid valve	No	Yes	IV drug abuse	Multiple septic pulmonary emboli; postoperative mediastinitis. Septic shock with gangrene of all extremities requiring amputation	Microaerophilic *Streptococcus, Bacteroides melaninogenicus*	Penicillin G given IV × 6 wks, gentamicin given IV × 2 wks	Prosthetic tricuspid valvulectomy; after 1 year, amputation of all four extremities; doing well
4	63	♀	None	Starr-Edwards prosthetic mitral valve (RHD)	No	Yes	?	None	Microaerophilic *Streptococcus*	Vancomycin hydrochloride given IV × 6 wks	Discharged asymptomatic, doing well 6 mos later
5	20	♀	None	Aortic	No	Yes	Multiple dental caries	None	Microaerophilic *Streptococcus*	Penicillin G given IV × 3 wks: gentamicin given IV × 5 days; penicillin V potassium (Pen-Vee K) by mouth × 2 wks	Discharged asymptomatic

TABLE 2.—*Clinical Characteristics of 7 Patients With Anaerobic and Microaerophilic Endocarditis at Rancho Los Amigos Hospital, January 1977 to June 1980 (Continued)*

Patient No.	*Age*	*Sex*	*Intravenous (IV) Drug Abuse (Duration)*	*Valve(s) Involved*	*Echocardiogram Positive**	*Cardiac Murmur*	*Probable Source of Infection*	*Complications*	*Blood Culture Isolates*	*Antibiotic Therapy*	*Outcome*
6	37	♀	Methylphenidate (1 yr)	Tricuspid & aortic	Yes	Yes	IV drug abuse, genito-urinary tract after vaginal delivery	Septic pulmonary emboli (recurrence of recent endocarditis)	*Bacteroides* sp, *Fusobacterium nucleatum*, *Fusobacterium* sp	Penicillin G given IV ×6 wks; clindamycin phosphate given IV ×6 wks	Discharged asymptomatic
7	28	♂	Heroin (44 days)	Tricuspid	No	Yes	IV drug abuse	Septic pulmonary emboli with cavitation	"Anaerobic *Eikenella corrodens*"	Penicillin G given IV ×6 wks	Discharged asymptomatic

IM=intramuscularly; IV=intravenously; RHD=rheumatic heart disease; SM=streptomycin sulfate.

*=Either valvular thickening, vegetations, or both.

infective endocarditis. The patients' ages ranged from 20 to 63, with the ages of the four drug abusers ranging from 22 to 38 (mean=31.2) and that of the three nonabusers from 20 to 63 (mean=44.3). Six of our seven patients were women. Two patients (Nos. 2 and 4) had a previous history of rheumatic heart disease (RHD) and one of these had a Starr-Edwards mitral valve prosthesis. Patient No. 3 had a recently treated endocarditis, which suggested a reinfection with other microorganisms after an uncomplicated vaginal delivery. All in all, three of the seven cases (43 percent) had preexistent valvular damage, with two patients having prosthetic valves in place. The tricuspid valve was infected in all four drug abusers, one of whom had a porcine tricuspid valve. One of these four patients had simultaneous involvement of the aortic valve. Two of the three nonabusers had involvement of the mitral valve (one of them had the Starr-Edwards mitral valve prosthesis) and the third had aortic valve involvement. The mouth was considered to be the source of infection in one patient (a nonabuser with multiple carious teeth) and another (a drug abuser) was presumed to have acquired the infection following vaginal delivery. All of the drug abusers had radiologic and clinical evidence of septic pulmonary embolism to the lungs, in two cases progressing to frank cavitation.

All three nonabusers had a single-organism IE with either an anaerobic or microaerophilic *Streptococcus*. Three of the four drug abusers exhibited polymicrobial IE; in each of these three patients blood cultures yielded three microorganisms simultaneously. One patient had purely anaerobic endocarditis, a second had one aerobe plus one microaerophile plus one anaerobe and the third patient had two aerobes plus one microaerophile.

Two patients (both drug abusers) required tricuspid valvulectomy for persistent fever and generally poor clinical response to antibiotic therapy. Patient No. 1 had sterile blood cultures before valvulectomy, which was done five weeks after antibiotic therapy was initiated. Cultures of the excised affected valve were sterile, but the patient's fever subsided after the surgical procedure while on the same antibiotic regimen. Another patient (No. 3) had a porcine tricuspid valve excised a week after antibiotic drugs were started when she had persistent fever, positive blood cultures and continued evidence of pulmonary embolism. Culture of the excised valve was

positive, and she had a stormy postoperative course characterized by mediastinitis (requiring tube drainage) and septic shock followed by gangrene necessitating amputation of all four extremities. She survived all these complications and repeat blood cultures continued to be sterile until discharge.

One patient (No. 4) with a microaerophilic streptococcal endocarditis involving a Starr-Edwards mitral valve prosthesis responded to a six weeks' course of antimicrobial therapy without need for prosthetic valve replacement. The remaining patients responded to courses of parenteral administration of antibiotic therapy ranging from five to ten weeks.

Comment

The 10.6 percent incidence of infective endocarditis due to anaerobic or microaerophilic microorganisms appears to be higher than the previously recorded incidence in the literature.[1] The high proportion of intravenous drug abusers in our patient population (66.6 percent) invited speculation of a possible relationship between the two observed events. However, a review of the literature on endocarditis in those who practiced intravenous drug abuse revealed a very low incidence of anaerobic or microaerophilic endocarditis (0 percent to 6 percent) in this patient population.[7-11] In addition, the incidence of anaerobic and microaerophilic IE was very comparable in our drug-abuser and non-drug-abuser populations. One interesting observation, however, was the confinement of anaerobic Gram-negative bacillary endocarditis to the drug-abuser group (patients No. 3, 6 and 7). Nastro and Finegold[12] reviewed the literature on anaerobic Gram-negative bacillary endocarditis and found only one drug abuser in 37 patients. It is possible that blood culture techniques more conducive to the isolation of anaerobic and microaerophilic microorganisms accounted for this relatively high incidence of anaerobic and microaerophilic IE in our patient population. Our low (6.1 percent) incidence of blood-culture-negative IE may also indicate a better recognition of these cases that would have otherwise been missed. The incidence of IE with negative blood cultures in the literature has generally ranged from 13 percent to 23 percent.[13] The relatively large amount of blood (10 ml) inoculated in 90 ml of broth culture medium theoretically could have facilitated the isolation of microorganisms from patients who may not consistently have at least one microorganism per milliliter of blood.

That all five of the patients (of the 66 cases at Rancho Los Amigos Hospital) with polymicrobial endocarditis were drug abusers was not surprising. Previous reviews have reported a varying incidence (2 percent to 9 percent) of polymicrobial endocarditis in drug addicts.[7-10] A review of polymicrobial bacteremia[14] also showed that three of 88 patients reviewed practiced intravenous drug abuse. These three patients were the only ones with endocarditis in that series.

An unexpected finding in our series was the fact that six of the seven patients (86 percent) in this series with anaerobic or microaerophilic endocarditis were women, although only 41 percent of the total IE population were. Analysis using the Fischer's exact test, however, revealed that the difference was not statistically significant ($P = .06$). In Nastro and Finegold's[12] review of anaerobic Gram-negative bacillary IE 65 percent of their population were men. In only one of our patients (No. 6) was the genitourinary tract a probable source of IE (that is, endocarditis occurred after a normal vaginal delivery).

One of our seven patients (No. 2) suffered from cerebral embolism. All four of our drug abusers had involvement of the tricuspid valve with concomitant septic pulmonary embolism. The incidence of serious systemic embolism originating from the left side of the heart in our patients is lower than the 60 percent incidence in Felner and Dowell's series.[1]

All seven of our patients survived their infection. Two patients required tricuspid valvulectomy to control it. In one of these patients (No. 3) mediastinitis developed, along with septic shock and gangrene of all four extremities requiring amputation; she nevertheless survived. Our 0 percent mortality is considerably better than the 21 percent to 46 percent mortality previously reported for IE due to anaerobic or microaerophilic bacteria.[1,12] The good response to antibiotic therapy in our patients is exemplified by patient No. 4, who was cured of prosthetic mitral valve endocarditis without resort to valve replacement. It should be pointed out, however, that none of our patients had *Bacteroides fragilis* endocarditis. This organism is frequently resistant to penicillin and may have contributed to the higher mortality in previous reports. In our limited experience, however, an-

aerobic and microaerophilic infective endocarditis due to organisms other than *B fragilis* may not necessarily imply a bleak prognosis.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

The Placenta: How to Examine It and What You Can Learn

Benirschke K

Contemporary OB/GYN
1981 Mar; 17:117-126

DISCIPLINES: Obstetrics, Family Practice, Pediatrics

READABILITY: Excellent

The author, known throughout the medical world for his knowledge of the placenta, warns us not to simply drop that organ into the bucket. He reminds us that a step-by-step examination of the placenta can give us retrospective information on the intrauterine life as well as predictions as to the future life of the infant.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Rubella Outbreak Among Hospital Employees

Strassburg MS, Imagawa DT, Fannin SL, et al

Obstetrics & Gynecology
1981 Mar; 57:283-288

DISCIPLINES: All Physicians (especially Hospital Administrators, House Staff, Public Health)

READABILITY: Very good

Today many young adults are rubella susceptible. Because of immunization of children, these people have never been exposed to wild virus infection. Outbreaks of rubella infections have occurred in this age group. The authors present excellent guidelines for testing and immunizing health workers who might expose women in early pregnancy.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Refer to: Deedwania PC: Calcium channel blockers (Medical Progress). West J Med 1982 Jul; 137:24-31

Calcium Channel Blockers

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Calcium (Ca^{++}) plays an essential role in many cardiovascular physiologic processes. Electrophysiologic properties of the sinus and atrioventricular nodes greatly depend on Ca^{++} ion influx. Also, Ca^{++} is the main link for excitation-contraction coupling of the myocardium. Ca^{++} channel blockers are a group of heterogeneous compounds that block the ionic influx of Ca^{++} into the myocardial and vascular smooth muscle cells. Because Ca^{++} plays a central role, it is not surprising that Ca^{++} channel blockers can produce profound alterations in cardiovascular functions. Recently several studies have shown these agents to be useful in the treatment of supraventricular tachyarrhythmia, variant angina, chronic stable angina and hypertrophic cardiomyopathy. In the future they may be found useful in preserving myocardium during cardiopulmonary bypass, in limiting infarct size and in the treatment of hypertension and congestive heart failure.

RECENTLY two calcium (Ca^{++}) channel blockers have been approved in the United States for the treatment of variant and chronic stable angina. Introduction of Ca^{++} channel blockers represents a considerable advancement in cardiovascular therapeutics and is indeed a welcome addition to the list of drugs available for the treatment of various cardiovascular disorders. The initial application of Ca^{++} channel blockers in the treatment of angina and supraventricular tachyarrhythmia represents only a few of the many indications (see Table 1) for which these agents are currently being investigated and have been found useful. In this article the role of Ca^{++} in cardiovascular physiology will be discussed and the basic pharmacology of Ca^{++} channel blockers as well as their clinical applications will be reviewed.

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Role of Ca^{++} in Cardiovascular Physiology

Ca^{++} ions play vital roles and are critical to the function of cardiac tissue and vascular smooth muscle. Ionic Ca^{++} has a key part in cardiac electrophysiologic processes, excitation-contraction coupling in myocardium and vascular smooth muscle and in control of energy storage and use.[1-3] Some of these important roles of Ca^{++} ions in various physiologic processes in the heart are illustrated in Figure 1.

Initially, on stimulation with a threshold stimulus, fast sodium (Na^{+}) channels open up at the cellular level and Na^{+} ions rush into the cell causing rapid depolarization (phase 0) (see Figure 2). This initial depolarization of the cell caused by inward movement of Na^{+} ions opens up the slow channels for Ca^{++} entry, allowing Ca^{++} ions to move inward during the plateau phase (phase 2) of the action potential.[3] Ca^{++}-carrying channels are called "slow channels" because they are several magnitudes slower than the "fast chan-

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
Ca^{++} = calcium
cyclic AMP = adenosine 3′:5′-cyclic phosphate
FDA = Food and Drug Administration
Na^{+} = sodium
PSVT = paroxysmal supraventricular tachycardia
SA = sinoatrial

TABLE 1.—*Potential Clinical Applications of Calcium Channel Blockers*

Cardiac arrhythmia
Vasospastic angina
Chronic stable angina
Hypertrophic cardiomyopathy
Systemic hypertension
Congestive heart failure
Pulmonary hypertension
Myocardial preservation

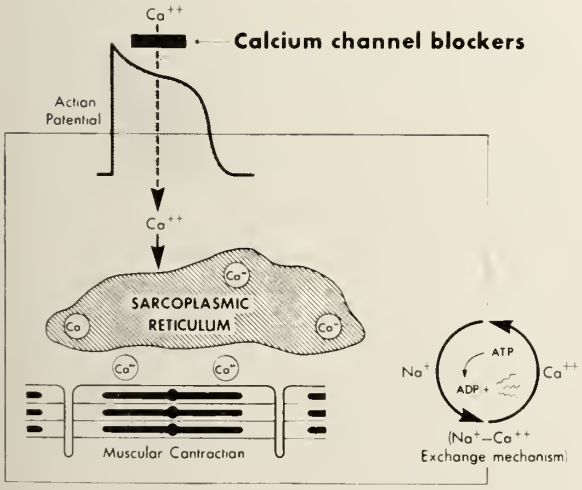

Figure 1.—Role of calcium in myocardial excitation-contraction coupling. Ca^{++} channel blockers act at the first step by blocking the influx of Ca^{++} ions during plateau phase of cardiac action potential. Ca^{++} = calcium, Na^{+} = sodium, ATP = adenosine triphosphate, ADP = adenosine diphosphate.

nels" of Na^{+}.[4,5] Slow channels depend on two kinds of stimuli—one is voltage-dependent and the other depends on activation of a protein kinase by adenosine 3′:5′-cyclic phosphate (cyclic AMP).[2,5] The Ca^{++} ions entering the cell during the plateau phase trigger release of larger quantities of Ca^{++} ions from sarcoplasmic storage sites. Once the intracellular concentration of Ca^{++} reaches above 10^{-7} M, it removes the inhibitory influence of the troponin-tropomyosin complex on the interaction between actin and myosin, and contraction ensues (see Figure 1). Thus the Ca^{++} entry into the cell

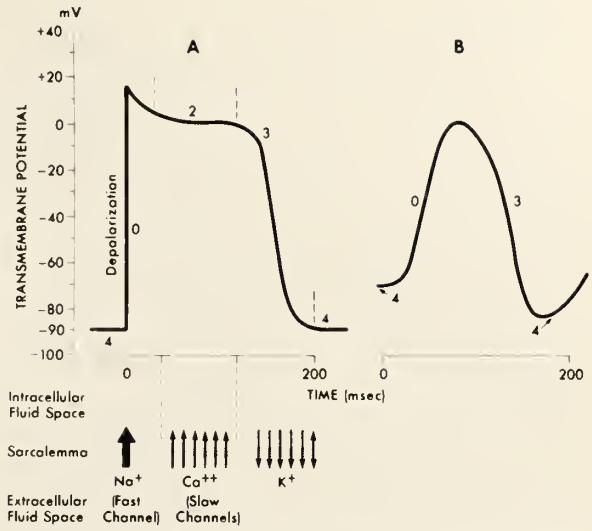

Figure 2.—Fast **(A)** and slow **(B)** cardiac action potentials in the heart. Calcium enters the cell during the phase 2 (plateau) of fast action potential **(A)** and slow action potential **(B)** depends mostly on Ca^{++} ions for its activation. msec = milliseconds, mV = millivolts, Na^{+} = sodium, Ca^{++} = calcium, K^{+} = potassium.

has an essential function in the excitation-contraction coupling in the myocardium.[1,6] Similarly, the extent of contraction of smooth muscle in the systemic and coronary vascular beds is dependent on the entry of Ca^{++} ions into the vascular smooth muscle cells.[1,6]

Ca^{++} Channel Blockers

Initially Ca^{++} channel blockers prenylamine and verapamil were introduced in Germany as coronary vasodilators for the treatment of angina pectoris.[7,8] Because these agents were found to produce inotropic and chronotropic effects that were opposite to those elicited by catecholamines, they were initially thought to be adrenergic blocking agents.[9,10] It was not until 1967 that pioneering studies of Fleckenstein and co-workers[11] showed that the action of these agents differed from those of beta blockers and was related to inhibition of the influx of Ca^{++} ions into myocardial cells. Consequently, the agents were named "Ca^{++} antagonists."[5] Later, in 1970 Fleckenstein[12] specified that Ca^{++} antagonists act by reversibly sealing specific Ca^{++} channels in the membrane of the mammalian myocardial cell.

These agents have been known variously as Ca^{++} antagonists, Ca^{++} channel blockers, Ca^{++} entry blockers, slow channel inhibitors and Ca^{++} inhibitors. But because they are known to antagonize Ca^{++} only at specific sites in the sarcolemma (the slow channel) and do not have a significant effect

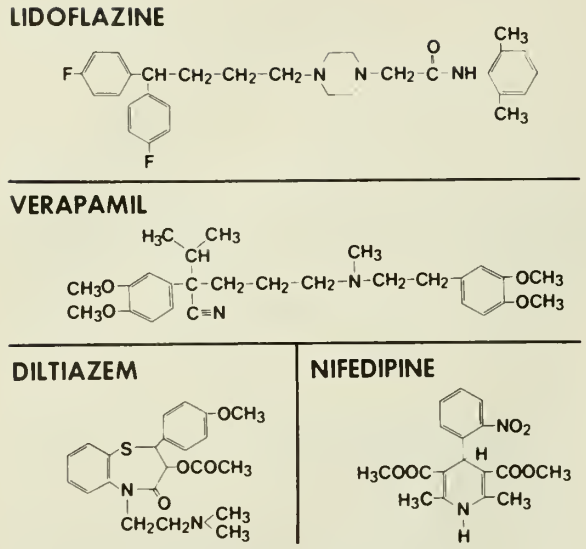

Figure 3.—Chemical structure of four different calcium channel blocking agents. Note the dissimilarity in their structure.

TABLE 2.—*General Properties of Calcium (CA^{++}) Channel Blockers*

May decrease cardiac pacemaker (SA nodal) activity
Usually increase AV nodal refractoriness
Cause myocardial excitation-contraction uncoupling (negative inotropic effect)
Reduce coronary vascular resistance (increase coronary flow)
Reduce systemic vascular resistance (decrease blood pressure)
Actions reversed by Ca^{++} or catecholamines

SA = sinoatrial, AV = atrioventricular

on a wide variety of Ca^{++} binding and transport systems, it is more accurate to refer to them as Ca^{++} channel blockers or slow channel inhibitors.[13]

Over the last two decades many new Ca^{++} channel blockers have been developed and introduced and now the list includes diltiazem, flunarizine, lidoflazine, nifedipine, niludipine, perhexiline, prenylamine, verapamil and D_{600} (the methoxy derivative of verapamil). However, most of the clinical studies in progress are evaluating nifedipine, diltiazem, verapamil and lidoflazine in the treatment of various cardiovascular disorders.

Pharmacology of Ca^{++} Channel Blockers

Ca^{++} channel blockers are a group of heterogeneous compounds. Although Ca^{++} channel blockers in general inhibit slow channel activity, unlike β-blockers these agents vary considerably in their chemical structure (see Figure 3) and overall actions in the cardiovascular system.[14,15] These differences are clinically important and may be related to quantitative differences in their ability to inhibit excitation-contraction coupling in cardiac tissue or vascular smooth muscle, effects on sinoatrial (SA) nodal automaticity or atrioventricular (AV) nodal conduction properties. Such variations would undoubtedly account for the difference in their net electrophysiologic effects, hemodynamic effects, overall therapeutic implications and adverse reactions. Table 2 shows some important general properties of Ca^{++} channel blockers.

Electrophysiologic Effects

Sinus and AV nodal cells have slowly rising action potential and are predominantly depolarized by inward movement of Ca^{++} ions (see **B** of Figure 2). Because of their dependence on Ca^{++} ions, automaticity of the SA and AV nodes and their velocity of conduction are greatly influenced by Ca^{++} channel blockers. Ca^{++} ions may also play a significant role in abnormal electrical states of cardiac cells.[16] When Na^{+}-dependent myocardial cells (atrial or ventricular muscle) are depolarized due to increased extracellular potassium (for example, in myocardial ischemia) or stretch, the Na^{+} channels become inactivated and the slow channels predominate.[16,17] These abnormally slow responses may play an important role in the genesis of cardiac arrhythmia.[18] It has also been proposed that triggered automaticity may occasionally be responsible for supraventricular and ventricular arrhythmias.[18] These abnormal response-induced arrhythmias and those due to triggered automaticity may be abolished by Ca^{++} channel blockers.[18,19]

Most studies of the cardiac electrophysiologic effects of Ca^{++} channel blockers have been conducted with verapamil.[20] In isolated preparation separated from extrinsic neural influences, verapamil decreases the spontaneous firing rate of the SA node.[20] This effect on the SA node is in part due to its direct inhibitory action on the Ca^{++} current and in part related to its noncompetitive antisympathetic actions.[21] However, in intact circulation these changes are greatly modified due to the drug's peripheral vasodilatory properties. The resulting hypotension causes reflex tachycardia, thereby neutralizing any direct negative chronotropic effects. In the AV node, verapamil and other Ca^{++} channel blockers (except nifedipine) slow AV nodal conduction and increase the duration of refractoriness without affecting the resting potential.[20-23] It is this property of Ca^{++}

TABLE 3.—*Electrophysiologic Effects of Ca^{++} Channel Blockers*

May suppress sinoatrial pacemaker activity
Prolong sinus node recovery time
No significant effect on intra-atrial conduction
Significant increase in AH interval (increased AV nodal delay)
Increase ERP and FRP of AV node
No significant effect on His ventricle interval
No effect on intraventricular conduction time
Variable effects on accessory pathway conduction (may shorten Kent's bundle ERP)

AH = atrio-His, AV = atrioventricular, ERP = effective refractory period, FRP = functional refractory period

channel blockers that makes them so useful in the treatment of supraventricular arrhythmia, especially AV nodal reentrant tachycardia.[20-24] In addition, verapamil has been found to decrease triggered automaticity or abolish abnormal depolarization in Purkinje's fibers.[18] Verapamil may shorten the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome and thus may be harmful in such patients.[25] Ca^{++} channel blockers have no significant effect on infranodal conduction times or on intra-atrial or ventricular conduction times. The electrophysiologic effects of Ca^{++} channel blockers are summarized in Table 3.

Hemodynamic Effects

Hemodynamic effects of Ca^{++} channel blockers are the net result of a complex interplay of simultaneous changes in heart rate, cardiac contractility, systemic vascular resistance and coronary blood flow.[26] Vascular smooth muscle tone in systemic and coronary arteries is greatly dependent on the intracellular concentration of Ca^{++} ions.[1,2] Ca^{++} channel blockers inhibit the influx of Ca^{++} ions and thus cause vasodilation and significant reduction in coronary and systemic vascular resistance.[26] Ca^{++} channel blockers have been found to counteract the coronary vasoconstriction induced by norepinephrine, angiotensin, methacholine, potassium (K^+) or barium chloride.[27] Ca^{++} channel blockers increase blood flow not only in coronary, but also in mesenteric and renal circulation. The systemic vasodilatory effects have been found to cause reduction in blood pressure and to increase reflexively myocardial contractility.[26] Ca^{++} channel blockers by their negative effect on excitation-contraction coupling directly decrease myocardial contractility.[6,26] However, this effect is mostly counterbalanced by the reflexive increase in contractility due to peripheral vasodilation caused by these agents.[28]

Although it is not possible here to describe various properties of individual Ca^{++} channel blockers, some general considerations and discussion of important differences is warranted. It must be reemphasized that though the common property of all Ca^{++} channel blockers is to block the entry of Ca^{++} ions into the cell, there could be considerable differences between their pharmacologic properties. Such differences in the pharmacologic properties of verapamil and nifedipine clearly account for the variability of their clinical application. Nifedipine depresses slow channel activity in the myocardium but has minimal depressant effect on the SA node or AV nodal conduction.[14] Such differences in the action of nifedipine as compared with those of verapamil may be due to the fact that nifedipine reduces the number of channels but does not alter the time course of the activation, inactivation or recovery from inactivation of the slow channel.[15] Verapamil, in contrast, has a marked influence on all these properties of the slow channels and in addition has some muscarinic blocking activity.[20] Because of the relative lack of electrophysiologic effects, nifedipine, unlike verapamil, is not useful in the treatment of supraventricular tachyarrhythmia. Verapamil, on the other hand, has less vasodilatory effect and may even have an adverse effect on myocardial contractility, especially in patients with preexisting left ventricular dysfunction.[28]

Clinical Applications

Because Ca^{++} plays a central role in many cardiovascular physiologic processes, it is not surprising that Ca^{++} channel blockers possess many important clinical properties (see Table 2). These actions can be useful in the treatment of a wide variety of clinical disorders that include (1) various cardiac arrhythmias, especially AV nodal reentrant tachycardia and atrial flutter and fibrillation; (2) myocardial ischemic syndromes, including Prinzmetal's angina (coronary artery spasm), chronic stable angina and possibly unstable angina; (3) hypertrophic cardiomyopathy, and (4) arterial hypertension. Although not firmly established, these agents have also been found useful in the treatment of congestive heart failure, in limiting myocardial infarct size and in myocardial preservation during cardiopulmonary bypass. The Food and Drug Administration (FDA)

has approved verapamil in its intravenous form for treatment of supraventricular tachyarrhythmia. Recently orally given verapamil and nifedipine have also been approved for use in Prinzmetal's and chronic stable angina. Diltiazem is still being evaluated by the FDA for approval as an anti-anginal agent.

In Cardiac Arrhythmia

Verapamil is by far the most widely studied Ca^{++} channel blocker in the treatment of cardiac arrhythmia.[20] It is considered the drug of choice for the treatment of paroxysmal supraventricular tachycardia (PSVT).[20-24] Several earlier studies have indicated that more than 80 percent of cases of PSVT can be promptly relieved by verapamil with very few side effects.[20-24] In a recent double-blind randomized crossover study, Waxman and associates[29] reported a 79 percent conversion rate in patients with PSVT and a 65 percent success rate in slowing the ventricular response in patients with atrial fibrillation or flutter.

In patients with AV nodal reentrant tachycardia, 5 to 10 mg of verapamil given intravenously terminates the tachycardia within two to five minutes of administration.[23] The mode of termination of PSVT by verapamil is not uniform, for it may occur as (1) abrupt termination, (2) initial slowing with eventual conversion to sinus rhythm, (3) transient atrial filbrillation followed by conversion to a normal sinus rhythm (NSR), (4) occurrence of premature ventricular contraction before conversion or (5) alteration in cycle length of the tachycardia before conversion.[20] Verapamil should be used with caution in patients with Wolff-Parkinson-White syndrome and atrial fibrillation because it can shorten the effective refractory period of the Kent's bundle, thus increasing the number of fibrillatory impulses that can traverse down the accessory pathway, possibly inducing ventricular fibrillation.[25] However, verapamil is considered to be an effective agent in the treatment of sustained supraventricular tachycardia in patients with overt and concealed Wolff-Parkinson-White syndrome; by slowing conduction at the AV node it breaks the reentrant circuit.[20] In patients with atrial flutter or fibrillation, verapamil has been found to effectively slow the ventricular response rate.

In a recent study[29] verapamil, when given as a bolus injection, was significantly more effective than placebo in slowing the ventricular rate in patients with atrial fibrillation. Klein and colleagues[30] recently evaluated the effects of verapamil in patients with chronic atrial fibrillation who were already receiving therapeutic dosages of digitalis. Verapamil substantially reduced the exercise-induced increase in the ventricular response rate in these patients.

Ca^{++} channel blockers are not very useful in the treatment of ventricular arrhythmia.[20-23] Some recent animal studies have shown these agents to be useful in controlling the arrhythmia produced by acute coronary occlusion.[31] Further studies are needed to establish their usefulness in arrhythmia produced as a result of myocardial ischemia.

In Anginal Syndromes

Angina is caused by an imbalance between myocardial oxygen demand and supply. Exertional angina usually occurs due to an excessive increase in myocardial oxygen demand in the presence of limited coronary artery blood flow. Angina at rest, however, has been shown in most cases to be due not to an increase in myocardial oxygen demand but rather to a primary reduction in oxygen delivery. Also, there is increasing evidence that whereas exertional angina is usually associated with fixed coronary artery obstructive lesions, angina at rest has been found often to occur as a result of coronary artery spasm and transient platelet aggregates.[32,33] Over the past several years there have been increasing belief in and evidence to suggest that coronary artery spasm plays a significant role in all varieties of myocardial ischemic syndromes.

At present the medical management of anginal syndromes is limited to the administration of β-blockers and nitrates. Patients may not fully respond to these agents, however, and occasionally intolerance develops due to side effects. In addition, β-blockers must be administered with caution in patients with bronchospastic pulmonary diseases or diabetes mellitus. Many recent studies have shown that Ca^{++} channel blockers are quite effective in the treatment of patients with coronary artery spasm and chronic stable angina.[34-50]

Ca^{++} channel blockers are unique agents for the treatment of anginal syndromes. Figure 4 shows that they possess hemodynamic properties comparable with those seen with nitrates and β-blocker combination therapy. Like β-blockers, these agents decrease myocardial oxygen demand by their negative inotropic and chronotropic effects. These effects are most apparent during exercise. In addition, Ca^{++} channel blockers are

COMPARATIVE ANTIANGINAL PROPERTIES OF VARIOUS AGENTS

Hemodynamic Parameter	Nitrates	β-Blockers	CA + + Channel Blockers
Heart rate	↑←	↓↓	↓
Blood pressure	↓	↓↓↓	↓↓
Myocardial contractility	→	↓	↓↑
Preload	↓↓	↑→	↑→
Afterload	↓	↑←	↓↓
Myocardial wall tension	↓	↑	
Myocardial O2 requirement	↓	↓	↓
Coronary vascular resist	↓↓	↑	↓↓
Coronary blood flow (O2 supply)	↑←	↓	↑
Subepi./subendo. blood flow	→↑	—	↑↑
Mitochondrial preservation	—	—	+

Figure 4.—Various important hemodynamic parameters governing myocardial oxygen demand and supply are shown and actions of conventional antianginal agents —nitrates and β-blockers—are compared with those of Ca^{++} channel blockers. Ca^{++} = calcium, O_2 = oxygen, resist = resistance, subepi = subepicardial, subendo = subendocardial, ↑ = increase, ↓ = decrease, → = no change, ← = no change, — = no information available, + = present.

potent coronary and systemic vasodilators, thus relieving coronary artery spasm, increasing coronary artery blood flow and decreasing the workload for the myocardium by reducing the afterload.

In Coronary Artery Spasm

Because Ca^{++} channel blockers are potent coronary vasodilators, there has been considerable interest in using them for treating patients with variant angina. Several studies have evaluated nifedipine, diltiazem, verapamil and perhexiline for the treatment of coronary artery spasm.[34-41] In a recently published multicenter study Antman and co-workers[34] summarized that in patients with coronary artery spasm, most of whom had previously been treated unsuccessfully with conventional antianginal medication, nifedipine eliminated the spontaneous attack and ST segment elevation in 63 percent of the patients, and in 87 percent of the patients the frequency of anginal attacks decreased by at least 50 percent. Rosenthal and associates[38] have found diltiazem to be quite effective also for the control of symptoms related to active coronary artery spasm. Similarly, verapamil has been effective in the treatment of exercise-induced coronary artery spasm.[39] A recent multi-institutional study in Japan evaluated the comparative clinical efficacy of nifedipine, diltiazem and verapamil in 286 patients with variant angina. Nifedipine, diltiazem and verapamil were effective in 94.0 percent, 90.8 percent and 85.7 percent, respectively.[40] In yet another study Waters and colleagues[41] provided objective evidence of efficacy by showing that nifedipine, diltiazem and verapamil can partially or completely block ergonovine-induced angina and ST segment elevation in most patients with variant angina. Thus there is little doubt that Ca^{++} channel blockers are quite effective in the treatment of patients with variant angina.

In Chronic Stable Angina

Currently available antianginal agents, β-blockers and nitrates, are ineffective or cause intolerable side effects in a substantial number of patients. Ca^{++} channel blockers seem to overcome some of these problems and appear to be promising therapeutic adjuncts for treating patients with stable angina.

The antianginal properties of Ca^{++} channel blockers have been discussed above. In summary, these agents are vasodilators and negative inotropic and chronotropic agents; thus they not only reduce myocardial oxygen demand, but may also increase the delivery of blood to ischemic areas. Various Ca^{++} channel blockers have been shown to control the exercise-induced increments in rate-pressure product and thus provide relief for exercise-induced angina. Finally, inappropriate vasoconstriction may play a part in causing chronic stable angina and Ca^{++} channel blockers, because of their coronary vasodilatory properties, are also effective in relieving such vasoconstriction.

Several recent studies have evaluated the clinical efficacy of Ca^{++} channel blockers in the treatment of stable angina patients. Worldwide experience using nifedipine in more than 4,000 patients for periods ranging from two weeks to three years showed beneficial results in patients with angina pectoris.[42] In a recently published multicenter double-blind, placebo-controlled study, Mueller and Chahine[43] summarized that nifedipine decreased the frequency of anginal attacks and the intake of nitroglycerin by about 50 percent; exercise tolerance was also noted to have increased significantly in the treated group. Similarly, verapamil, as compared with a placebo, has been found to decrease the frequency of angina and prolong exercise duration.[44] Hossack and Bruce[45] have recently reported that high dosages of diltiazem (240 mg a day) substantially increased the duration of exercise and the time to the first onset of angina in patients with chronic stable angina.

Several studies have compared the efficacy of

Ca^{++} channel blockers with other conventional antianginal agents. Kaltenbach[46] has shown that nifedipine, propranolol, pindolol and nitroglycerin used in comparable dosages were equally effective in controlling the degree of ST segment depression during exercise tolerance testing. Kimura and co-workers[47] have shown nifedipine to be as effective as isosorbide dinitrate in treatment of patients with angina pectoris. In a recent study Johnson and associates[48] compared the relative efficacy of propranolol and verapamil in patients with stable angina pectoris. Verapamil was found to be equally or more efficacious in alleviating symptoms of angina pectoris and the need for nitroglycerin. A recent report by Leon and colleagues[49] showed that the combination of verapamil and propranolol produced a greater antianginal effect than that achieved by either drug alone and may be considered suitable treatment for patients with severe angina refractory to single-drug therapy. Further studies are needed to establish the safety of such a combination because both propranolol and verapamil have a depressant effect on SA and AV nodes.

Ca^{++} channel blockers may be useful in patients with angina refractory to conventional antianginal therapy. In a recent study Moses and co-workers[50] have found nifedipine to be efficacious in the treatment of rest angina patients with obstructive coronary artery disease who were previously refractory to propranolol and nitrate therapy. Although further studies are needed to determine long-term efficacy and adverse effects of Ca^{++} channel blockers in the treatment of angina pectoris, there is no doubt that these agents will prove to be important adjuncts to currently available regimens.

In Hypertrophic Cardiomyopathy

Administration of β-blocking drugs is now considered to be the treatment of choice for patients with hypertrophic cardiomyopathy. Occasionally such treatment is inadequate in controlling symptoms and a patient usually needs to be referred for surgical intervention. Ca^{++} channel blockers now provide an effective alternative in such refractory patients. Rosing and associates[51] have shown verapamil to be extremely effective in controlling symptoms of patients with hypertrophic cardiomyopathy and long-term studies[52,53] have shown that treatment with verapamil improves their exercise capacity considerably. Although the exact mechanism of its beneficial action in patients with hypertrophic cardiomyopathy is not known, it may be due to the drug's negative inotropic effect, combined with its ability to increase the rate of ventricular filling.[52,54]

Potential Applications

Although not well established, Ca^{++} channel blockers have been found useful in systemic hypertension,[55] pulmonary hypertension,[56] and congestive heart failure.[57] Experimental studies[58-60] during acute coronary occlusion have shown Ca^{++} channel blockers to have a myocardial protective effect and that they limit the degree of ischemic damage in experimental animals. These data need to be established further and clinical studies be done before any conclusions can be drawn regarding the clinical usefulness of these agents in acute myocardial infarction.

Summary

The development of Ca^{++} channel blockers indeed represents an important milestone in cardiovascular treatment. Verapamil in its intravenous form is now available for use in the treatment of supraventricular tachyarrhythmias. Oral preparations of verapamil and nifedipine have recently been approved by the FDA for treatment of variant angina and chronic stable angina refractory to conventional therapy. Several Ca^{++} channel blockers are being evaluated for treatment of patients with unstable angina, acute myocardial infarction and other ischemic syndromes. In the future, these agents may also prove to be of clinical use in hypertension, congestive heart failure and in myocardial preservation.

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Turner's Syndrome

FORTY-FOUR YEARS AGO Henry Turner recognized the combination of sexual infantilism, webbed neck and cubitus valgus to be a distinct entity.[1] In subsequent years, gonadal dysgenesis was defined as part of the syndrome and many patients were found not to be Barr body (sex chromatin) negative.[2] It was determined 21 years after Turner's original description that the chromosome composition in typical patients with Turner's syndrome was missing one sex chromosome (45,X).[3] A variety of X chromosomal abnormalities and mosaicism were also found to be associated with Turner's syndrome, and the specific congenital malformations (short stature, shield chest, webbing of the neck, peripheral lymphedema at birth, short fourth metacarpals, hypoplastic nails, multiple pigmented nevi, coarctation of the aorta and so forth) became known as the Turner stigmata.[4]

Although much information is now available about Turner's syndrome in infancy, childhood and adolescence, much less is known about the natural history of this syndrome in adulthood.

During the past eight years we have developed a multidisciplinary clinic for patients with Turner's syndrome designed to provide care on an ongoing basis and to study the natural history of the syndrome.* We have records and access to more than 200 patients (two thirds of whom are under 25 years of age) and have formulated an approach to long-term care, screening for medical complications and treatment of certain complications. This review of Turner's syndrome is directed toward practicing physicians.

Cytogenetics and Clinical Correlations

Turner's syndrome occurs in 1 out of 4,000 to 1 out of 10,000 live births, giving an incidence of 1 out of 2,500 female birth .[4,5] Approximately 98 percent to 99 percent of pregnancies with Turner's syndrome abort spontaneously and approximately 10 percent of fetuses from pregnancies that have spontaneously aborted have Turner's syndrome.[5] It is therefore a relatively common chromosomal syndrome at conception that is highly lethal in utero. In our experience, approximately a third of patients with Turner's syndrome are diagnosed in the newborn period, a third in childhood and a third in late teens when they fail to go through puberty.

The minimal diagnostic criterion for Turner's syndrome is an abnormal karyotype in which a portion or all of one of the X chromosomes is

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ABBREVIATIONS USED IN TEXT

DES = diethylstilbestrol
IQ = intelligence quotient
TSH = thyroid-stimulating hormone

missing.[6] Almost all patients will also have gonadal dysgenesis and short stature.

In the 1950's and 1960's Barr body (sex chromatin) studies were used to diagnose Turner's syndrome. The presence of a Barr body in cells from a buccal smear was said to rule out the diagnosis of Turner's syndrome. However, the buccal smear in mosaics and in patients with an isochromosome X often show Barr body material, resulting in misdiagnosis. There is now a consensus that banded chromosome studies must be done when the diagnosis of Turner's syndrome is considered and chromosomes should be counted in 50 cells to rule out mosaicism. The buccal smear should no longer be used as a diagnostic test. Most often cytogenetic studies in patients with this syndrome are done by culture of peripheral leukocytes, but fibroblasts can be used and should be if the suspicion of Turner's syndrome is strong and leukocyte studies are normal.

A variety of chromosomal constitutions (Table 1) are seen in Turner's syndrome. Although most studies reporting the frequency of specific chromosomal compositions in this condition have biased ascertainment, it appears that half of patients with Turner's syndrome have a "straight" 45,X (45,XO in the old literature) karyotype in peripheral blood. From 12 percent to 20 percent of patients have an isochrom some X (duplication of one arm of the X with loss of the other arm).[7] Mosaicism, the presence of two or more chromosomally different cell lines in the same person, is found in 30 percent to 40 percent of Turner's syndrome patients.[8] Mosaicism may be demonstrated in some patients on culture of peripheral leukocytes alone. In others, cultures of skin fibroblasts may be necessary in addition to blood studies to show mosaicism. It is estimated that 10 percent to 15 percent of patients are 45,X/46,XX mosaics and 2 percent to 5 percent of patients are 45,X/46,XY mosaics.[7] Special staining techniques (banding) may be required to detect some of the more subtle interstitial chromosome deletions.

The most important reason to look carefully for mosaicism in patients with suspected Turner's syndrome is to identify those with 45,X/46,XY karyotypes, as these persons have an increased risk for the development of gonadoblastomas in their gonadal streak.[9] Patients with Turner's syndrome who have not been karyotyped and those whose "45/X" diagnosis is on the basis of a negative buccal smear should be karyotyped and evaluation carried out for the presence of a Y chromosome.

Clinical Correlations

There appear to be no pathognomonic clinical features of Turner's syndrome, but rather a pattern of malformations, any one of which should raise suspicion of this diagnosis (see Figures 1 and 2). Even such standard phenotypic features as amenorrhea and short stature are seen in only 80 percent to 90 percent of all patients with this syndrome.[10] Table 2 summarizes the clinical features in our patients. This table repre-

TABLE 1.—*Chromosomal Constitutions in Our 127 Patients With Turner's Syndrome*

Chromosome	*Number of Patients*	
45,X	71	
	71	(55.0%)
46,XiX	4	
46,XiX(q)	3	
46,XXq⁻	2	
46,XXp⁻	1	
46,XX/45,X	17	
46,XX/45,X/47,XXX	3	
46,XX/45,X/45,XiX	1	
46,XX/45,Xp⁻	1	
45,X/46,XiX	2	
45,X/46,XiXq	4	
45,X/46,XXp	1	
45,X/47,XXX	1	
45,X/46,XrX	5	
45,X/46,XrX/47,XXrX	1	
45,X/46,XXiX/47,X,XiX,XiX	1	
45,XiX/46,XXiX	1	
	48	(37.2%)
46,XY/46,XiX	1	
46,XY/45,X	4	
	5	(3.9%)
XO/XO+marker	1	
XO/XX+marker	1	
XO/XX/45,XX (G monosomy)	1	
XO/XXt(X,12)	1	
XO/XX+8/XX+8+8/XX+7	1	
	5	(3.9%)

i = isochromosome; q = long arm; — = deletion; p = short arm; r = ring; t = translocation

sents biased sampling and there have been no studies of the phenotypic features of the syndrome in which patients were selected by karyotype only, rather than by specific physical findings. Most of the surveys were done many years ago when only more clinically obvious patients were detected.

In our experience, any combination of physical features can be seen with any combination of X chromosome abnormality and severity of clinical features cannot be correlated with karyotypic findings. For example, we have been observing several patients who have 45,X karyotypes in all tissues tested and yet have normal stature. In general, however, the loss of the short arm (p) of the X chromosome appears to be most frequently associated with phenotypic findings of Turner's syndrome.[11] Patients who are mosaics for Turner's syndrome appear to have fewer phenotypic stigmata, and patients with isochromosome of the short arm of the X (46,XXi[p]) often appear phenotypically normal.[10]

The diagnosis of Turner's syndrome should be

Figure 1.—Four-year-old girl with Turner's syndrome. Note somewhat broad chest, prominent ears and ptosis, but otherwise normal proportion. There is no pronounced neck webbing or edema.

Figure 2.—A 35-year-old woman with Turner's syndrome. Note increased carrying angle of arms, broad flat chest and sexual infantilism, but the lack of pronounced neck webbing or peripheral edema.

considered in any female patient who has short stature, gonadal dysgenesis, amenorrhea or peripheral lymphedema in the newborn period. It is better to do too many chromosome studies than to miss this diagnosis because of the medical and psychological implications.

Differential Diagnosis of Turner's Syndrome

Short stature, sexual infantilism and peripheral lymphedema are the clinical hallmarks of the Turner's syndrome. Short stature is an easily recognizable clinical feature that may be seen at birth and is usually obvious before the onset of puberty. A growth rate of less than 4 cm a year during childhood is an indication for evaluation of short stature; the diagnosis of Turner's syndrome should be suspected in all short girls (Table 3). Unexplained primary or secondary amenorrhea should also always raise suspicion of this syndrome. Lymphedema, primarily in infant girls but also at other ages, should alert a clinician to the possibility of this disorder.

The most important and confusing entity in the differential diagnosis of Turner's syndrome is Noonan's syndrome.[12-15] Although Noonan's syndrome is thought to be a specific autosomal dominantly inherited disorder, other less well-defined entities have also been given this label. Patients with Noonan's syndrome have often been described as "male Turners," but in fact the autosomal dominantly inherited Noonan's syndrome occurs in both sexes. Affected persons have short stature, webbed neck, cubitus valgus, pectus deformities, midfacial hypoplasia[12] and other stigmata of Turner's syndrome. Many male patients with Noonan's syndrome have been reported to have cryptorchidism and decreased fertility.[13] Some female patients with Noonan's syndrome have reproduced, others are reported to have gonadal dysgenesis.[14] Approximately 50 percent of patients with Noonan's syndrome have congenital heart disease. The cardiac lesions of Noonan's syndrome are usually right-sided, most often pulmonic valvular stenosis,[15] whereas the cardiac lesion associated with Turner's syndrome is usually coarctation of the aorta, a left-sided lesion not commonly seen in Noonan's syndrome. Mild to moderate mental retardation or "dullness" is common in Noonan's syndrome, whereas this feature is uncommon in Turner's syndrome.[16] Most important, people with Noonan's syndrome have normal chromosome constitutions. A buccal smear is not adequate to differentiate between Turner's and Noonan's syndromes; karyotyping of peripheral blood leukocytes is necessary.

There are other medical disorders that also must be differentiated from Turner's syndrome. These are listed in Table 3. A carefully taken history, physical examination and appropriate laboratory and radiologic studies will readily

TABLE 2.—*Clinical Findings in 100 of Our Patients With Turner's Syndrome*

	45,XO (n=59) Number (percent)	*Mosaic n=41 Number (percent)*	*Total n=100* Number (percent)*
Lymphedema	31 (53)	5 (12)	36 (36)
Abnormal nails	31 (53)	12 (20)	43 (43)
Ptosis	8 (14)	3 (7)	11 (11)
Myopia	8 (14)	6 (15)	14 (14)
Epicanthal folds	22 (37)	5 (12)	27 (27)
Webbed neck	30 (51)	11 (27)	41 (41)
Low hairline	39 (66)	15 (37)	54 (54)
Shield chest	39 (66)	16 (39)	55 (55)
Coarctation of aorta	7 (12)	2 (5)	9 (9)
Heart murmur	27 (46)	16 (39)	43 (43)
Abnormal ears	33 (56)	15 (37)	48 (48)
Chronic otitis media	35 (59)	18 (44)	53 (53)
Gastrointestinal and feeding problems	22 (37)	15 (37)	37 (37)
Cubitus valgus	33 (56)	22 (54)	55 (55)
Other skeletal abnormalities	20 (34)	20 (50)	40 (40)
Renal abnormalities	19 (32)	8 (20)	27 (27)
Hypothyroidism	5 (8)	3 (isoX)	8 (8)
Mental retardation†	0 (0)	0 (0)	0 (0)

*Only 100 patients with enough clinical information for tabulation were included. In those patients not personally examined, we were forced to make the assumption that if the feature was not commented on, it was not present.

†Mental retardation associated with additional abnormality (autosomal chromosome abnormality or familial mental retardation).

TABLE 3.—*Differential Diagnosis for Turner's Syndrome*

Short stature
- Noonan's syndrome
- Familial short stature
- Dyschondrosteosis (Leri-Weill syndrome)
- Brachydactyly E
- Growth hormone deficiency
- Hypothyroidism
- Glucocorticoid excess
- Multiple pterygium syndrome
- Klippel-Feil anomaly
- Short stature due to chronic disease

Amenorrhea or failure to begin puberty
- Pure gonadal dysgenesis
- Stein-Leventhal syndrome
- Primary/secondary amenorrhea

Lymphedema
- Hereditary congenital lymphedema
- AD—Milroy's type
- AR—Lymphedema with recurrent cholestasis
- AD—Lymphedema with intestinal lymphangiectasia

AD = autosomal dominant; AR = autosomal recessive

differentiate these entities from the chromosomally abnormal Turner's syndrome.

Hormone Replacement Therapy

Most girls with Turner's syndrome will require exogenous hormone replacement for the establishment of secondary sex characteristics. The timing of induction of puberty and the doses of estrogen and progesterone vary with each person. We use the lowest possible dose of natural estrogen that will promote and maintain secondary sex characteristics and begin therapy when it becomes socially important for the girl to go into puberty.

Approximately 10 percent of nonmosaic women with Turner's syndrome (usually those with structural abnormalities of the X chromosome, including small deletions of the short arm[17]) and 20 percent of mosaics[4,18] will have spontaneous menses (usually irregular and ceasing prematurely) and may not require medication to initiate puberty. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) determinations may be useful before beginning hormone-replacement therapy to determine whether the ovaries are functioning adequately for hormone production. If they are, the patient should be allowed to go through puberty spontaneously. After age 10, those girls with functional ovaries will be expected to have normal-for-age levels of gonadotropins, whereas those without residual ovarian tissue will have prominently elevated gonadotropin levels. Gonadotropin levels are usually low in all girls during midchildhood, even in those patients with gonadal dysgenesis, and thus serum levels may not be indicative of gonadal failure in that age group.[19]

Hormone-replacement therapy in Turner's syndrome used to be delayed as long as possible to allow for maximum linear growth. Alexander and co-workers[20] showed ultimate height gain was not affected by the time of initiation of hormone therapy. Thus, we begin replacement therapy when a patient desires to appear more like her teenage peers, but with consideration for the familial timing of the age of onset of puberty.

We use an initiating dose of 0.3 mg of conjugated estrogens (Premarin) taken on days 1 to 25 of a 28-day cycle. This is usually continued for six months to a year, during which time the development of pubic hair and breasts should occur. This regimen mimics normal physiology in that the first four or more menstrual cycles in normal women are usually anovulatory, with little or no production of progesterone.

After this initial period, the conjugated estrogen dose is increased to 0.625 mg on days 1 to 25, with the addition of 10 mg of a progesterone (medroxyprogesterone acetate, Provera) to be taken concomitantly on days 15 to 25. Withdrawal menstrual flow on this dose of estrogen may not occur every month. However, if a patient has more than three consecutive cycles without bleeding, she may need a higher dose of estrogen. A scraping of the lateral vaginal wall for a maturation index will indicate whether there is inadequate estrogen effect. If this is found, alternating one month of 0.625 mg of estrogen with one month of 1.25 mg may be indicated. This should rarely be necessary, and most patients will be adequately maintained on a regimen of cycling with 0.625 mg of Premarin and 10 mg of medroxyprogesterone acetate (Depo-Provera). Although we prefer Premarin because of the many years of experience with its use, an equivalent dose of any other estrogens can be used in replacement therapy, with the exception of diethylstilbestrol.

Any intermenstrual bleeding in patients over 30 years of age should be investigated with an adequate endometrial biopsy, including both cytologic and histologic studies.[21] In younger patients one or two such episodes may be simply observed. Persistent breakthrough bleeding should be thoroughly investigated in any patient of any age with Turner's syndrome. If there has been a history of long-term unopposed estrogen use or diethylstilbestrol exposure, endometrial biopsy should be done before introducing the preferred ratio of estrogen to progesterone replacement therapy.

With this regimen the danger of uterine cancer over a lifetime of hormone replacement seems to be low. Although it is not known whether women with Turner's syndrome are at increased risk for endometrial cancer, there are theoretical reasons to assume they may be because of the frequent occurrence of obesity and the long-term exogenous hormone therapy.[22] Until more is known, it may be appropriate to do endometrial biopsies every other year in patients with this syndrome after age 40 if hormonal replacement therapy is continued.

The use of unopposed ethinyl estradiol is known to cause endometrial hyperplasia in patients with Turner's syndrome.[23] The occurrence of endometrial cancer, however, has been associated in Turner's syndrome patients almost exclusively with the use of diethylstilbestrol (DES)

and, in all but one case,[24] a progestational agent was not used. In our opinion, DES has no place in the therapy of patients with Turner's syndrome and cycling with progestational agents should be part of any long-term replacement therapy.

It is not clear if and when hormone replacement therapy should be stopped. It may be appropriate to withdraw therapy at the usual age of menopause in normal women. Conversely, the possible prevention of osteopenia in some patients may warrant lifelong treatment (L. Speroff, MD, personal communication, 1981; see "Skeletal" section). This is an area that needs more study before specific recommendations can be made.

Some patients will voluntarily discontinue hormone therapy. If vaginal atrophy and dyspareunia occur, the use of a vaginal estrogen cream may alleviate symptoms. The absorption of estrogens from the vaginal mucosa may result in circulatory hormone levels equivalent to those achieved with oral intake.[25] This, coupled with the lack of a progesterone agent, may cause endometrial hyperplasia with a risk for adenocarcinoma of the uterus. Therefore, older patients receiving long-term therapy with creams should be monitored for endometrial hyperplasia, as should patients receiving unopposed estrogen-replacement therapy taken by mouth.

Fertility

Fertility is a real, albeit rare, possibility in women with Turner's syndrome.[18] A recent summary brings to 11 the number of conceptions in 45,X chromosome women without apparent mosaicism, though in only a third of these patients were more than two tissues karyotyped to look for mosaicism.[26] In women with X chromosome mosaicism nearly 100 pregnancies have been recorded.[27] In both groups of women, mosaic and nonmosaic, pregnancy occurs almost exclusively in those having either spontaneous menses or secondary sexual characteristics, or both.

There are two major considerations in the care of patients with Turner's syndrome found to be fertile: (1) They are more likely to begin menopause at an earlier age[26] and (2) there is a high percentage of pregnancy wastage and abnormal offspring born to these women. Even allowing for the inherent bias of single case reports, an increased risk of miscarriage, stillbirths and chromosomally abnormal births remains. Combining reported cases, the risk of spontaneous abortion is about 50 percent.[18,27] There are no reports of karyotypes of the abortus material. Of live births, nearly a third have been chromosomally abnormal. Most have had sex chromosome mosaicism and were born to mosaic mothers. However, there are four reported cases of trisomy 21 infants delivered of mothers with mosaic Turner's syndrome.[18,28-31] Therefore, amniocentesis should be offered to pregnant women with Turner's syndrome, realizing that if sex chromosome mosaicism is found, the counseling for this condition (shared by the pregnant mother) and a decision by the parents for or against abortion may prove extremely difficult.

TABLE 4.—*Risk for Gonadoblastoma in Patients With Turner's Syndrome With a Y Chromosome**

Percentage of Risk (percent)		*Age (years)*	*Percentage of Risk (percent)*		*Age (years)*
2.0	at	10	16.0	at	20
5.0	at	14	27.5	at	30

*From Similia et al,[35] Boczkowski et al,[36] Teter and Boczkowski[37] and Miller et al.[38]

Counseling about fertility is one of the more stressful situations for a patient and her parents. We tell patients that they are likely to need hormones to help them go into puberty and that they are most likely to have their children by adoption. We avoid the use of the words sterile, barren and childless. We also tell an adolescent patient (and often the parents of patients of any age) that they will be capable of normal and satisfactory sexual relations, interpersonal relations and family life. We stress that they will have the same options as anyone to marry or not, to work or not, to have children by adoption or not.

Cancer Risk

Individuals with Turner's syndrome are at a higher risk than the general population of tumors of the reproductive system developing.[32] The major risk for malignancy in this syndrome is for gonadoblastoma, which occurs almost exclusively in those persons mosaic for a Y chromosome (Table 4). Although there is a notable rise in this risk at puberty, gonadoblastomas develop in a high percentage of 45,X/46,XY patients in early childhood, warranting evaluation and removal of streaked gonads during preschool years.[33-36] This also avoids the potential of virilization seen in many 45,X/46,XY patients at puberty. Any patient with Turner's syndrome in whom virilization spontaneously occurs should have a laparoscopy or exploratory surgical procedure to look for

intra-abdominal testicular streaks and gonadoblastoma. Although the tumor may be unilateral at the time of operation, the risk for recurrence on the opposite side is high.[37] Therefore both gonads or streaks should be completely removed.

There are isolated case reports of dysgerminomas, seminomas and teratomas in patients with Turner's syndrome and combinations of these tumor types have been found in a single gonadal streak.[38] The risk for adenocarcinoma of the uterus is discussed in the section on hormone replacement.

A number of Turner's syndrome patients with Crohn's disease and ulcerative colitis have been reported.[39-43] Ulcerative colitis is associated with an increased risk for gastrointestinal malignancy; however, there have been no reports of gastrointestinal tumors in women with Turner's syndrome.

There are case reports of this syndrome being associated with eosinophilic adenoma, thymoma, leukemia, neural crest-derived tumors and other types of cancer, but there is no evidence to suggest that these occur in Turner's syndrome at an incidence above that in the general population.[44]

Growth and Skeletal Abnormalities

The skeletal findings in Turner's syndrome can be characterized as undifferentiated bone dysplasia associated with shortness of stature. Osteoporosis is also said to be seen.[45]

On the average, shortness of stature in this syndrome is of prenatal onset; average birth length is 47 cm (18 in).[8] Girls remain small, growing along or below the third percentile until age 8 or 9 when the average growth curve begins to fall below the third percentile. The shortness of stature becomes more obvious when girls with this syndrome fail to show an adolescent growth spurt. This results in a further decrement in the growth curve. Adult heights are usually between 122 and 152 cm (4 and 5 feet). Women with a mosaic chromosome or an isochromosome X constitution tend to be taller than women with a 45,X karyotype.[4] Familial height also plays a role in determining ultimate height; taller parents have taller daughters with Turner's syndrome.[46]

The bone age in these female patients is usually within normal limits until 12 to 14 years of age when, without pubertal hormones, there is no adolescent growth spurt and bone fails to mature. In women who receive no hormone therapy, the epiphyses usually fail to fuse until the 20's.[46,47] Despite this long period of growth, final adult height is still well below normal. Estrogen therapy results in a growth spurt as puberty is initiated but apparently does not limit final adult height.

There is controversy about the use of hormonal agents to stimulate growth in patients with this syndrome. Attempts to increase adult height in Turner's syndrome with the use of anabolic steroids have been reported.[48-53] Although an initial growth spurt does occur, more rapid fusion of epiphyses also results and final height does not show significant gain.[20,48,49] Recently, therapeutic trials using anabolic steroids with and without growth hormone while carefully monitoring epiphyseal fusion have shown promising results.[50-52] The follow-up periods are short however and final assessment of these therapies has not been made.[53] In our opinion, treatment with anabolic steroids should be reserved for experimental protocols with appropriate controls and adequate follow-up periods. At least one author recommends explaining the controversy to patients and

TABLE 5.—*Commonly Reported Roentgenographic Changes**

- Hand
  - Drumstick distal phalanges
  - Short fourth metacarpals
  - Carpal sign: change in angulation of the carpal bones
  - Shortening of all hand bones
  - Madelung's deformity
- Feet
  - Similar to hands
  - Pes cavus
- Knees
  - Lateral dislocation of the patellae
  - Hypoplastic patellae
  - Irregularity of tibial metaphysis and epiphysis
  - "Mushroom" projections, medial surface of the proximal tibial metaphyses (medial tibial condyle)
- Spine
  - Scoliosis
  - Lack of lumbar lordosis
  - Schmorl's nodes (abnormalities of cartilaginous endplates)
  - Hypoplasia of the arch of the atlas
  - Shortening of anteroposterior diameter of vertebral bodies
- Ribs
  - Thin
  - Developmental abnormalities
- Pelvis
  - Android configuration (50 percent)
  - Occasional widening of symphysis pubis
- Skull
  - Midfacial hypoplasia
  - Deepening of posterior cranial fossa
  - Widely spaced mandibular rami

*From Brook et al[46] and Risch et al.[55]

allowing a patient to make the decision about anabolic steroid therapy.[50]

There is a flattening and distortion of the epiphyses in patients with Turner's syndrome most noticeable in the wrists, hands, knees and spine. The more common and more clinically striking bony abnormalities include the following: short fourth metacarpals, midfacial hypoplasia and cubitus valgus (increased carrying angle). Table 5 lists the common roentgenographic abnormalities.[45,54]

The *midfacial hypoplasia* seen in many patients due to relative undergrowth of the maxilla may be severe enough to result in eustachian tube dysfunction and a high arched palate. Recurrent bouts of suppurative otitis media with secondary hearing loss is a common occurrence in children with Turner's syndrome. Treatment with insertion of indwelling drainage tubes may be necessary. A high arched palate, also part of the midfacial hypoplasia, may cause feeding difficulties in infancy requiring the use of special feeding nipples. Most of our patients reported problems with feeding in infancy.

Osteoporosis is said to occur with increased frequency and at an earlier age in female patients with Turner's syndrome.[45,54] Evidence for this contention includes increased radiolucency of the bones with coarse trabeculation in a widespread distribution, decreased bone mineral content[55] and decreased cortical width measurements.[56,57] However, the radiolucency of bone and the coarse trabeculations can be seen in patients with this syndrome in childhood and do not necessarily worsen with age. These abnormalities, therefore, may reflect a primary defect in bony structure, in the bone matrix, and not a result of the demineralization of osteoporosis. There is apparently no correlation of these changes with the karyotype or phenotype.

Previous methods of determination of osteopenia—cortical bone width and radiographic appearance—are indirect and not necessarily reliable in patients with underlying bony dysplasias. In our experience osteoporosis has not been proved to occur more commonly in Turner's syndrome, nor is it clear that our patients have had an increased number of fractures. Park[56] noted improvement in radiographic findings with estrogen therapy, but others have not.[54,58] There have been no studies of estrogen replacement for bony abnormalities in women with Turner's syndrome who have been observed over a long period.

Cardiovascular Changes (Including Lymphatic Alteration)

Most studies citing the frequency of occurrence of specific cardiac malformations in Turner's syndrome report on series of nonkaryotyped patients and include those with other diagnoses such as Noonan's syndrome (patients with a Turner phenotype but with a normal chromosomal constitution).[58,59] When only karyotype-proved cases of Turner's syndrome are evaluated, the most common malformation found is coarctation of the aorta, which may be preductal or postductal.[13] Coarctation of the aorta may occur in as many as 15 percent of patients with Turner's syndrome but is often not clinically important. It appears that coarctation of the aorta is seen with higher frequency (50 percent) in patients with a 45,X karyotype.[4]

There have been several case reports of dissecting aneurysm of the aorta in Turner's syndrome patients with coarctation.[60-63] Aortic valve disease has also been reported.[64] Less common malformations include ventricular septal defects, atrial septal defects, dextrocardia and hypoplastic left heart. The diagnosis of Turner's syndrome should be considered in any female infant with a hypoplastic left heart (even with no other clinical features of the syndrome) and chromosome studies obtained. Pulmonic stenosis (which occurs more commonly in Noonan's syndrome) is occasionally seen in patients with 45,X Turner's syndrome.

Vascular malformations include intestinal telangiectasias, hemangiomas and lymphangiectasia.[32,65,66] While these are relatively infrequent, they should be considered in any patient with Turner's syndrome and gastrointestinal bleeding. Surgical resection of areas of the bowel may be required for persistent bleeding from gut hemangiomas. In our experience, estrogen supplementation is helpful in controlling bleeding in some patients but may exacerbate the bowel disease in other patients. As ulcerative colitis and Crohn's disease occur more frequently in Turner's syndrome, gastrointestinal bleeding may indicate primary bowel disease. Protein-losing enteropathy due to gastrointestinal lymphangiomas have been reported also.

There have been several reports[67-69] of an *increased number of renal arteries* in most patients with Turner's syndrome examined. Of normal people, 20 percent to 40 percent will have multiple renal arteries whereas in persons with this

syndrome, the incidence of multiple renal arteries approaches 90 percent. No correlation of the number of arteries with either hypertension or fibromuscular hyperplasia of the renal arteries has been found.

In the pediatric population of patients with Turner's syndrome, coarctation of the aorta is the most common cause of *hypertension*. The blood pressure often returns to normal in these patients after early surgical repair of the coarctation. In adult patients, hypertension occurs with increased frequency even when coarctation of the aorta and renal parenchymal and renal vascular disease have been eliminated as causes.[58,68,69] In our adult patients with Turner's syndrome, the incidence of hypertension approached 30 percent. This ranges from mild, 140/90 persistently, to severe, 150/110 or higher. We have observed a notable association of high blood pressure with obesity.[69] No other factors, including family history, age, karyotype, renal status, hormone therapy or cardiovascular malformations, correlated with the presence or absence of hypertension in our adult patients with Turner's syndrome. We currently recommend weight reduction and low salt intake for all hypertensive women with Turner's syndrome once other causes (for example, coarctation, renal disease) of hypertension have been eliminated. Whether this will have a salutary effect on arterial blood pressure in these patients remains to be seen.

Atherosclerosis has not been found at an early age in women with Turner's syndrome despite early and sustained hormone replacement therapy.[70] Although the use of estrogens has been associated with thromboembolic phenomena in normal women, we have not seen vascular complications in our patients.

Congenital transient *lymphedema* is seen in 80 percent of newborns with Turner's syndrome.[15] This usually resolves in childhood; however, recurrent lymphedema of the extremities is seen in some patients. This may be cyclical and exacerbated by estrogen therapy. The lymphedema is almost always secondary to congenital hypoplasia of lymphatic channels and is not an indication of congestive heart failure.[71] Conventional therapy such as surgical intervention, support hose and salt restriction may be helpful.

Renal Findings

Renal abnormalities seen include structural and positional anomalies (Table 2). Approximately 60 percent of all patients with Turner's syndrome have a renal structural anomaly,[72] compared with 10 percent of all normal births.[73] The kidney anomalies in this syndrome rarely result in renal malfunction.[74]

Horseshoe kidneys are seen in about 20 percent of patients. Duplication of the collecting ducts in the presence or absence of a horseshoe kidney is seen in another 20 percent. Malrotation of the kidney is found in about 15 percent of all patients with Turner's syndrome. A variety of other anomalies are reported.[75] There is no known correlation between a specific karyotype and a specific renal anomaly. It has been suggested that an intravenous pyelogram be done on all patients with Turner's syndrome.[72] Ultrasound examination may be equally useful for detecting structural abnormalities. Patients with collecting system anomalies are apparently at increased risk for urinary tract infections and should be monitored by yearly cultures of urine.

Skin, Nails, Hair

Dermatologic features of Turner's syndrome include specific dystrophic findings: abnormal dermatoglyphics, pterygium colli and small hypoconvex nails, as well as an increase in the occurrence of "normal" variants, such as nevi, seborrhea, xerosis, hirsutism and keloid formation.

The pterygium colli, or webbed neck, appears to result from the in utero persistence of embryonic lymph sacs with resultant severe lymphedema.[76] This usually resolves before birth, leaving redundant folds of skin. The nuchal hairline is lower and the ears may be cupped anteriorly with upturned lobules. The amount of neck webbing is extremely variable, occasionally requiring plastic surgical repair. As there may be an increased tendency for hypertrophic scarring (keloids) cosmetic surgical procedure is best done by a plastic surgeon. The risk of keloid formation may be a contraindication to piercing ears[50]; however, most of our patients have had no problems with such scarring. Hypoplastic hypoconvex nails may also be a result of prenatal edema. Some of our patients have reported problems with upward direction of growth of the toenails. These dystrophic nails may need to be surgically corrected to allow wearing of normal shoes.

Pigmented nevi occur more commonly in patients with Turner's syndrome and are primarily a cosmetic problem. There is no evidence of an increased rate of malignant degeneration of these

moles; however, removal should be undertaken with care because of potential keloid formation.

A substantial number of our patients have severe seborrheic dermatitis of the scalp and marked xerosis (dryness) requiring vigorous emollient therapy and antiseborrheic shampoos. Topical application of steroids to the scalp is occasionally required.

Facial hirsutism is rarely a problem in Turner's syndrome. The vellus hairs of the arms and legs may be more darkly pigmented and coarser than usual and often have a patchy distribution. Axillary and pubic hair is often scanty even after hormone therapy and this occasionally causes embarrassment for adolescent and young adult patients. Reassurance about sexuality and about the normal variation in body hair among women is often important. Thinning of scalp hair and male pattern baldness is seen in some patients. We have found a number of hair styles that can be more flattering and disguise abnormal nuchal hair patterns. The potential for cosmetic therapy is often overlooked in patients with Turner's syndrome and a physician needs to directly address these issues when appropriate.

Autoimmune Disease

There have been isolated case reports of autoimmune disorders in women with Turner's syndrome, but only hypothyroidism, diabetes mellitus and inflammatory bowel disease have been shown to occur more frequently than in the general population.[77]

Acute Hashimoto's thyroiditis occurs infrequently, but frank hypothyroidism on an autoimmune basis is seen in approximately 20 percent of adult women with Turner's syndrome.[77,78] Pai and associates[78] found elevated thyroid antibody titers in 9 of 15 of their patients over 10 years of age (60 percent). Antithyroglobulin antibodies have been found in 20 percent of adult patients studied. In our experience, antithyroglobulin antibodies and hypothyroidism can be seen in association with any karyotype, but patients with an isochromosome X appear to be at the highest risk for acute Hashimoto's thyroiditis and Graves' disease.[70,77-80]

Antithyroglobulin antibody testing is carried out in all patients at two-year intervals. If antibodies are present, thyroid-stimulating hormone (TSH) levels are tested yearly. If TSH levels are elevated, thyroid-replacement therapy is started. This protocol usually averts the development of frank hypothyroid symptoms or goiter formation.

Diabetes mellitus occurs more frequently in women with Turner's syndrome (2 percent to 15 percent) as compared with age-matched controls.[81,82] Of patients with the syndrome 25 percent to 60 percent have diabetic levels on oral glucose tolerance tests without frank diabetes.[82] Monitoring these patients with yearly routine analyses of urine for glycosuria is probably adequate screening for diabetes mellitus. Antibodies to islet cells have not been measured in diabetic patients with Turner's syndrome. However, none of 38 nondiabetic women with the syndrome had islet cell antibodies (RM Blizzard, MD, personal communication, 1981).

Inflammatory bowel disease, both regional enteritis and ulcerative colitis, appears to have an increased incidence in patients with Turner's syndrome.[43] There has been no study of antibodies to intestinal basement membrane in these patients.

Central Nervous System

Mental Retardation

Early reports of women with Turner's syndrome suggested a high prevalence of mental retardation.[1,58,83-85] All of these studies had sampling biases. As recently as 1976, the frequency of mental retardation in this syndrome was quoted as 10 percent.[15]

We have shown in a study of 206 patients that mental retardation is almost always associated with the presence of other chromosomal abnormalities in addition to an abnormal or absent X chromosome.[16] The prevalence of mental retardation in those individuals with Turner's syndrome and karyotype abnormalities limited to the X chromosome appears to be no greater than that in the general population. The presence of mental retardation in a patient with Turner's syndrome requires further workup. We recommend banded chromosome studies of several tissues be done in these patients for the purpose of finding autosomal abnormalities and marker chromosomes. Also, detailed family histories should be elicited, looking for other family members with mental retardation.

Learning Deficits

In 1962 Shaffer[86] showed that patients with Turner's syndrome had average or above-average verbal intellectual skills, but many were deficient in skills requiring perceptual motor organization.

Wechsler performance intelligence quotient (IQ) scores (map reading, figure drawing, geometry, arithmetic) averaged 20 points lower than the verbal IQ scores for each person.

There is no convincing correlation of the specific space-form learning deficits in patients with Turner's syndrome with karyotype or phenotype. All of the studies dealing with learning problems in this syndrome have involved small numbers of patients and some have come to contradictory conclusions.[87-90]

When present, the learning deficit is not incompatible with academic success. Many girls initially thought to be slow have "caught up" academically. Of our adult patients 80 percent have completed at least four years of college. Occasionally special education may be required to help circumvent specific learning disabilities. In our experience, open discussions with the families about approaches to overcoming these problems have been most helpful.

Psychiatric Abnormalities

A number of psychiatric disturbances have been reported in patients with Turner's syndrome, including anorexia nervosa,[91-99] manic-depressive illness,[100] paranoia[101] and schizophrenia.[102]

A small increased risk for anorexia nervosa appears to be present in these patients.[98,99] Thus, it has been suggested that all women seen for anorexia nervosa be checked for karyotype. Only one woman in our patient population has so far needed treatment for anorexia nervosa.

Other psychiatric disturbances seen in patients with Turner's syndrome do not seem to occur with a frequency greater than in the general population, but careful studies remain to be done. It is not at all clear whether specific personality types are consistently seen with this syndrome, nor what the causal factors for specific psychiatric problems might be.[103]

Management of Adult Patients

As girls with Turner's syndrome approach adulthood, reaffirmation of femininity and normal sexual capabilities becomes important. Gynecologic examination of patients to insure an adequate vaginal canal is advisable. The use of a vaginal estrogen cream for atrophy and dryness may be necessary. The concept of having children by adoption should be reiterated and support provided by helping patients contact local adoption agencies. More than half of our adult patients are married; 60 percent of these have adopted children.

Little is known about the natural history of Turner's syndrome in adult women. There is a paucity of information about long-term follow-up of these patients. However, women with this syndrome are at risk for a number of medical complications: thyroid disease, obesity, hypertension, malignancy, bowel disease, vaginal atrophy and dyspareunia. We have outlined in this summary our approach to some of these problems. Awareness of the increased risk for these problems allows for the practice of preventive medicine.

With appropriate and sensitive management of medical and psychosocial issues, girls born with Turner's syndrome should have every opportunity to lead fully functional and satisfying lives. Communication of this attitude to patients and their families by their physicians and other health care professionals is of the utmost importance.

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Surgical Circumcision of Neonates: A History of Its Development

Grossman E, Posner NA

Obstetrics & Gynecology
1981 Aug; 58:241-246

DISCIPLINES: Obstetrics, Gynecology, Pediatrics, Family Practice, General Surgery

READABILITY: Excellent

A fascinating article. The authors trace the evolution of circumcision techniques and the instruments used from Biblical times to the present day. They conclude that circumcision of male infants is here to stay.

—E. R. W. FOX, MD
Coeur d'Alene, ID

In-Hospital Maternal Mortality in the United States: Time Trends and Relation to Method of Delivery

Petitti DB, Cefalo RC, Shapiro S, Whalley P

Obstetrics & Gynecology
1982 Jan; 59:6-12

DISCIPLINES: Obstetrics, Gynecology, General Surgery, Family Practice

READABILITY: Very good

This carefully done retrospective review of the statistics of 3.5 million deliveries performed in 654 hospitals nationwide between 1970 and 1978 showed (1) a gradual reduction in the mortality rate for both vaginal and cesarean deliveries and (2) a mortality rate that was at least twice as high but no more than four times as high for cesarean sections as compared with vaginal deliveries.

E. R. W. FOX, MD
Coeur d'Alene, ID

Burn Injury: Rehabilitation Management in 1982

Helm PA, Kevorkian CG, et al

Archives of Physical Medicine and Rehabilitation
1982 Jan; 63:6-16

DISCIPLINES: Plastic Surgery, Physical Medicine and Rehabilitation, General Surgery

READABILITY: Good

This is a comprehensive review of the physical, kinetic, cosmetic and psychosocial problems and their solutions in the restoration of burn patients. It deals with all levels and grades of injury, and all facets of restorative care.

—GLENN G. REYNOLDS, MD
San Jose, CA

Refer to: Locksley RM: The lowly diphtheroid: Nondiphtheria corynebacterial infections in humans—Medical Staff Conference, University of California, San Francisco. West J Med 1982 Jul; 137:45-52

The Lowly Diphtheroid: Nondiphtheria Corynebacterial Infections in Humans

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *This Medical Staff Conference will be presented by Dr. Richard Locksley, a graduate of the University of California, San Francisco, medical residency program and former Chief Resident at the Moffitt Hospital. Rich is now a fellow in infectious diseases at the University of Washington. He will address the clinical spectrum of diseases caused by "the lowly diphtheroid."*

DR. LOCKSLEY:† Corynebacteria are Gram-positive, nonmotile, nonsporulating bacilli that often appear pleomorphic on Gram stain. The name, derived from Greek (*koryne* = club, *bakterion* = a little rod), refers to the characteristic club-shaped tapered appearance of *Corynebacterium diphtheriae* grown on Loeffler's media. Although human infection by *C diphtheriae* has been well described, this has not been true of the nondiphtherial corynebacteria. These organisms, usually designated "diphtheroids," are ubiquitous in the environment (soil, fresh and salt water); they are commensals of humans, animals and plants.[1]

Whereas the pathogenicity for animals of several of these *Corynebacterium* sp has been established,[2,3] their capacity for causing human infections has been infrequently reviewed.[4-7] There are several reasons:

First, there is still taxonomic confusion regarding the grouping and speciation of these organisms.[1] On the basis of cell-wall constituents, including mesodiaminopimelic and mycolic acids, corynebacteria are more closely related to the genera *Mycobacterium* and *Nocardia* than to other Gram-positive bacilli. Speciation is more problematic. Many laboratories do not identify *Corynebacterium* sp beyond excluding *C diphtheriae*. Several of these species can be frustratingly inactive biochemically if testing is done in the absence of serum- or lipid-supplemented media. Further, of 221 *Corynebacterium* strains isolated from burn patients, fully 90 percent remained unspeciated by criteria available in 1973.[8] The Centers for Disease Control (CDC) continue to organize unspeciated *Corynebacterium* into alphabetized groupings on the basis of fermentative and oxidative reactions. This foresighted approach has resulted in the recognition of the group JK organ-

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Dr. Locksley's work is supported by a training grant (AI 07044) from the National Institute of Allergy and Infectious Diseases.

TABLE 1.—*Characteristics Differentiating Coryneform Bacteria That Cause Infection in Humans**

	Genera				
	Corynebacterium	*Listeria*	*Propionibacterium*	*Erysipelothrix*	*Kurthia*
Aerobe/facultative anaerobe	+	+	−	+	+
Motility	−	+ (21°C)	−	−	+ (35°C)
Catalase	+	+	+	−	+
Hemolysis on blood agar	Variable (β)	β	−	α	−
H_2S in triple sugar iron or Kligler iron agar	−	−	−	+	−

H_2S = hydrogen sulfide, + = positive, − = negative.

*Adapted from Lipsky et al.[7]

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
CSF = cerebrospinal fluid
PVE = prosthetic valve endocarditis
SICU = surgical intensive care unit

isms as pathogens responsible for specific clinical syndromes.[9]

Second, because they are members of the normal flora, *Corynebacterium* sp are usually regarded as contaminants when they are isolated from clinical specimens. Diphtheroids grew from 10 percent and 16 percent of more than 30,000 blood cultures collected at the Mayo and Cleveland Clinics, respectively.[10,11] Whereas most of these isolates were insignificant, the preconception of diphtheroids as contaminants can lead to dire clinical consequences.

Third, some *Corynebacterium* sp require prolonged incubation or specialized growth conditions, or both. Isolations may be missed unless blind subcultures and stains are made from nonturbid blood culture media. In the analyses of blood culture isolates previously mentioned, the median time for detection of diphtheroids was nine days.[10,11] Pathogenic isolates may require similarly prolonged periods before detection.

Other bacteria causing human infection may appear coryneform on Gram stain and must be distinguished from *Corynebacterium* (Table 1). In the appropriate clinical setting (neonates, alcoholic patients, cerebrospinal fluid [CSF] specimens) "diphtheroid" isolates should be suspected of being *Listeria*. The rapidly growing mycobacteria, *Mycobacterium fortuitum* and *Mycobacterium chelonei*, may also stain as club-shaped Gram-positive bacilli. Other pleomorphic organisms that may be confused with *Corynebacterium* by Gram stain include *Actinomyces, Arachnia, Bacterionemia, Bifidobacterium, Eubacterium, Nocardia, Rothia* and *Streptomyces*. *Bacillus* sp are spore-forming.

Despite the difficulties in morphology and taxonomy, several distinctive clinical syndromes caused by some of the speciated diphtheroids have emerged. Although some of these observations are based on limited numbers of case reports, these cases are probably vastly underreported due to the difficulties previously enumerated. A comprehensive review, including historical and microbiological characteristics of these organisms, together with their pathogenicity for animals and humans, has recently appeared,[7] to which the reader is referred for information beyond the clinical reports summarized here.

The organisms are grouped according to their likely reservoir as a pathogen to humans (Table 2). They either are acquired after contact with animals (zoonosial) or are components of the endogenous flora. Some may be nosocomially acquired as well. It must be emphasized that these groupings are only probable; the true position of these organisms in the human ecosphere has been incompletely defined. Nevertheless, this organization may be clinically useful.

Zoonoses

Corynebacterium equi

C equi is primarily an animal pathogen. Suppurative bronchopneumonia (horses), cervical adenitis (pigs) and pyometra (cattle) have been described. The usual portal of entry is the respiratory tract. Organisms persist in contaminated soil.

There are eight reported cases in humans. The patients, four men and four women, ranged in age from 18 to 52 years.[12-18] Five of them reported exposure to animals, usually horses. All had severely compromised cell-mediated immunity; five had hematologic malignancy (two Hodgkin's, two other lymphoma, one acute lymphocytic leukemia), two were renal-transplant recipients and

TABLE 2.—*Sources of Nondiphtheriae Corynebacterial Infections in Humans and Their Probable Pathogens*

Zoonosially acquired
Corynebacterium equi
Corynebacterium ovis
(Corynebacterium pseudotuberculosis)
Corynebacterium ulcerans
Corynebacterium pyogenes
Corynebacterium bovis
Normal flora
Corynebacterium xerosis
Corynebacterium pseudodiphtheriticum
(Corynebacterium hofmannii)
Corynebacterium hemolyticum
? Group JK
Nosocomially acquired
Group JK
? *C xerosis*
? *C bovis*

one was receiving immunosuppressive therapy for plasma cell hepatitis. When tested, patients were anergic to skin tests and had normal immunoglobulin and leukocyte levels. Two had had splenectomy.

The eight cases presented with pneumonitis, frequently showing nodules on chest x-ray studies and usually occurring in the upper lobes (five/eight). Cavitation (five/eight) and empyema requiring chest tube drainage (two/eight) were complications. The diagnosis was established from cultures of specimens from lung biopsy (three), blood (three), bronchoscopic washings (four), pleural fluid (two), skin lesions (two) or nodes (one). The organism was rarely recovered in sputum (two/eight).

Two patients died of progressive infection; six were cured. One had surgical resection of a pulmonary lesion only. The other five all relapsed with pulmonary (four) or cutaneous lesions (two), or both, after receiving antibiotics for 10 to 20 days. Cure required prolonged antibiotic therapy. One patient, who relapsed with multiple subcutaneous abscesses and fistulae and a pharyngeal membrane—all of which grew *C equi*—was treated with erythromycin for six months.

Although *Corynebacterium parvum* (reclassified as *Propionibacterium acnes*) has been used to potentiate immunity in patients with malignancy, none of the patients who had hematologic malignancies had objective tumor responses during the course of their *C equi* infections.

C equi grows well on standard media, producing pink, mucoid colonies. It is frequently acid-fast. The organism has coccoid morphology on agar and bacillary forms in liquid media. It variably reduces nitrate and hydrolyzes urea but is inactive against carbohydrates. It is rarely isolated from normal human flora even among compromised hosts.[15]

Erythromycin and gentamicin are most active against *C equi* by in vitro susceptibility testing.[19] Therapy should be prolonged with erythromycin given orally after the acute illness has subsided.

C equi must be distinguished from other acid-fast organisms that can cause cavitating pneumonia in compromised hosts, including *Mycobacterium, Nocardia* and *Legionella micdadei.*

Corynebacterium ovis (Corynebacterium pseudotuberculosis)

Sheep are the most common animal reservoir for *C ovis,* which may cause suppurative lymphadenitis, skin abscesses and bronchopneumonia in these animals. Cattle and horses are also infected. Horse infections are prevalent in Nevada and California; the animals have hindfoot or truncal abscesses, usually in the late summer or fall.

The eleven reported human cases[20-28] occurred in previously healthy persons; ten of the patients were men. Seven cases occurred in Australia and two in the United States (Washington, California). Six had direct contact with sheep, four had contact with other farm animals and one consumed raw milk. The latter was the presumed source of infection because mammary gland infections have been described in cows.

Ten patients presented with localized lymphadenopathy (axilla, five; inguinal, three; cervical, two). Four were asymptomatic, but six noted systemic symptoms (fever, malaise) and a tender lymph node. Either surgical drainage or excision, or both, with administration of antibiotics, was required for cure. Persistent drainage and sinus tract formation recurred in five of ten cases, and reexcision and prolonged antibiotic therapy were necessary for recovery.

Pathologically, nodes were replaced by necrotizing granulomas. *C ovis* was grown from the tissue and usually visualized in the specimen by microscopy. The histologic appearance resembled tuberculous lymphadenitis, cat-scratch disease and lymphogranuloma venereum.

The 11th patient was a veterinary student working with horses who presented with a left lower lobe pneumonia and 31 percent eosinophilia.[21] A transbronchial biopsy showed all the features of eosinophilic pneumonia, but the specimen from

transtracheal aspiration grew a pure culture of *C ovis*. He recovered after a 14-day course of erythromycin. No other pulmonary pathogens could be implicated. The only other case that occurred in the United States (cervical adenitis) was also accompanied by eosinophilia (10 percent).[20]

C ovis grows slowly on blood agar (where it may be β-hemolytic) and best on Loeffler's media. Colonies can mimic *C diphtheriae* on Tindale's media, but *C ovis* is distinguished by its ability to hydrolyze urea. *C ovis* is closely related to both *C diphtheriae* and *Corynebacterium ulcerans*. All of these organisms are capable of phage-inducible diphtheria toxin production,[29] but no toxigenic strains of *C ovis* have been described from human cases. *C ovis* produces an exotoxin that causes dermonecrosis in animals.[30]

C ovis is sensitive to most antibiotics. Erythromycin, tetracyline and penicillin have been used successfully.

C ulcerans

C ulcerans is probably a commensal of horses and cattle. It can cause bovine mastitis and has been isolated from raw milk.

Most human isolates are pharyngeal and are generally from asymptomatic children living in rural areas. Only rarely is there an accompanying pharyngitis or tonsillitis.[31] Most reports are from England and describe typically sporadic cases among persons with a history of exposure to livestock or of raw milk ingestion.

C ulcerans can also produce phage-inducible diphtheria toxin, and occasional patients have presented with a full-blown diphtheria syndrome. Of 122 human strains evaluated in one series, 43 (35 percent) were toxigenic.[29] However, a diphtheria syndrome is rarely seen with *C ulcerans* infection, perhaps due to the lower levels of toxin produced by toxigenic strains as compared with *C diphtheriae*.[32] *C ulcerans* also produces a dermonecrotic exotoxin.[32]

The organisms grow best on Loeffler's or Tindale's media where the colonies resemble *C diphtheriae*. It is distinguished from *C diphtheriae* by its positive urease and inability to reduce nitrate and from *C ovis* by its ability to ferment starch.

Erythromycin is the therapeutic agent of choice. Diphtheria antitoxin may be administered in cases resulting from toxigenic strains.

Corynebacterium pyogenes

C pyogenes is a commensal and an occasional pathogen of cattle, sheep and pigs. It generally causes suppurative local infections but dissemination with metastatic abscesses has been described.[2,3] Infections in humans are uncommon and no characteristic clinical syndrome has emerged.[33-38] Endocarditis has been reported.[34]

C pyogenes shares with *Corynebacterium hemolyticum* several features that are atypical when compared with the other *Corynebacterium* sp. These two organisms are catalase negative and ferment lactose. Both are β-hemolytic on blood agar. Unlike *C hemolyticum, C pyogenes* does not show metachromatic granules after staining with alkaline methylene blue. *C pyogenes* produces a hemolysin and a dermonecrotic exotoxin.

Corynebacterium bovis

C bovis is a commensal of the bovine udder. The organisms can cause bovine mastitis and may contaminate milk.[2,3]

Only seven human cases have been reported[39,40]; a history of animal exposure was not obtained in most of these. Three cases had infections of the central nervous system (one meningitis, one epidural abscess with possible meningitis, one infected ventriculojugular shunt). A case of mastoiditis was also reported. The patient with the CSF shunt infection had hypocomplementemia and mesangiocapillary glomerulonephritis; *C bovis* antigen was seen in the glomeruli by immunofluorescence. Diphtheroids have been increasingly incriminated in cases of "shunt nephritis," but unfortunately speciation of these corynebacterial isolations has not been done.[41-43] Two cases of prosthetic valve endocarditis due to *C bovis* occurred four and seven months postoperatively. One patient died. The patients had had valve replacement at the same hospital within a few weeks of one another, raising the question of nosocomial acquisition of the organism. The final case was a chronic cutaneous ulcer at the site of an injury that was incurred in a butcher's shop, which may have been the source of the organism.

C bovis grows on standard media but biochemical testing should be carried out using serum- or lipid-supplemented media. Isolates have been variably sensitive to penicillin. All have been sensitive to erythromycin. In one case there was synergy between erythromycin and rifampin.[40]

Probably Endogenously Acquired

Corynebacterium xerosis

C xerosis is a member of the normal flora of the skin and nasopharynx. It was originally felt to be a cause of acute conjunctivitis but this is no longer believed.

In 1977 the cases of 11 patients from whom *C xerosis* was isolated over a two-month period were reported from a surgical intensive care unit (SICU) in California.[44] The patients had severe multisystem disease and most had received broad-spectrum antibiotics. Five patients were infected (four with pneumonia, one with wound infection); six patients were colonized (wounds, sputum). Three patients had bacteremia; two died. All of the organisms were sensitive to penicillin, but none were sensitive to nafcillin and only 68 percent and 53 percent of isolates were sensitive to clindamycin and gentamicin, respectively. Because most of the patients in the SICU had received the latter three antibiotics, the authors suggested that overgrowth and invasion by *C xerosis* occurred following antibiotic pressure in these compromised hosts. The bunching of these cases in time and space suggests that nosocomial spread may have occurred, but the authors felt this unlikely because the antibiograms and biochemicals of the isolates were different.

Two cases of prosthetic valve endocarditis occurring 1 and 14 months postoperatively have also been reported.[45] In one, cultures required 8 to 15 days to become positive. Annular invasion and dehiscence required replacement of the prosthesis in both cases. One patient died of a cerebral embolus. Both patients had received prophylaxis with methicillin and oxacillin. Although in both cases the isolates were sensitive to penicillin, one isolated organism was tolerant (minimal inhibitory concentration [MIC] = 0.17, minimal bactericidal concentration [MBC] = 20 μg per ml).

C xerosis grows well on standard media. All strains reduce nitrate and ferment glucose, fructose, galactose and sucrose. Penicillin or vancomycin, possibly with an aminoglycoside, would seem to be the drugs of choice, but antimicrobial susceptibility testing should guide therapy.

Corynebacterium pseudodiphtheriticum (Corynebacterium hofmannii)

C pseudodiphtheriticum is a normal commensal of the human nasopharynx. Human infections, some poorly characterized, have all been cases of endocarditis on abnormal valves.[4,46] Of seven reported cases three involved prosthetic valves, two occurred in patients with rheumatic valvular disease, one was in a patient with congenital heart disease and one patient had had preceding endocarditis. Interestingly, five of the seven patients had previous or coexistent endocarditis with another organism. Three died—two had prosthetic valve endocarditis and one died in the preantibiotic era.

C pseudodiphtheriticum grows on standard media. The organism reduces nitrate and hydrolyzes urea but is inactive in carbohydrates.

C hemolyticum

C hemolyticum is a commensal of the normal human skin and nasopharynx. Since the initial description by MacLean and associates in 1946[47] of organisms isolated from patients evacuated from the Pacific Islands after World War II, there have been several reports implicating this agent in pharyngitis and cutaneous lesions. Most large series have been from the tropics[48] or England,[49,50] but cases from the United States have been described.[51]

Among 150 cases of *C hemolyticum* pharyngitis from series where age and sex have been delineated, most occurred in older children and young adults (74 percent less than 25 years old) and more often in women and girls (63 percent). The clinical presentation closely mimics streptococcal pharyngitis; follicular tonsillitis, fever, leukocytosis and submandibular adenopathy are common, but a pseudodiphtheritic membrane has also been described.[51] Septicemia has been reported.[52] In reports from England pharyngitis was accompanied by a pruritic maculopapular or scarlatiniform rash over the trunk and extremities in almost 50 percent of cases. Desquamation can occur. Disease in household contacts has been described. In English reports *C hemolyticum* was isolated in pure culture in 130 of 139 cases (94 percent); in the tropics coisolation of other pharyngeal pathogens *(C diphtheriae, Streptococcus pyogenes)* occurred in 35 of 72 patients (49 percent).

Because careful viral and *Mycoplasma* cultures have not been carried out in most of these reports, there remains some doubt about the pathogenicity of *C hemolyticum* in pharyngitis. MacLean and co-workers[47] were unable to produce symptoms by spraying the organisms on the pharynx of volunteers. However, its isolation in pure culture from cases with pharyngitis, disappearance from

the throat coexistent with both antibiotic therapy and symptomatic improvement, the recognition of culture-positive symptomatic recurrences and the demonstration of high titers of specific antibody all suggest that this organism may be a cause of pharyngitis. The disease is likely vastly underreported, as most pharyngeal corynebacteria are not speciated and are disregarded unless a physician suspects *C diphtheriae*.

Approximately 50 cutaneous lesions from which *C hemolyticum* has been isolated have been reported, primarily from the tropics.[47-49] A coexisting pathogen, usually *S pyogenes or Staphylococcus aureus,* has been isolated from 75 percent of the cases, though *C hemolyticum* has shown the most abundant growth. Patients with cutaneous lesions (ulcers, cellulitis) were typically older men. Rash was not described.

Miscellaneous reports include two cases of brain abscess in young boys[53,54] and two cases of osteomyelitis.[47,55]

Like *C pyogenes, C hemolyticum* is catalase negative and β-hemolytic. Growth and hemolysis on sheep blood agar are poor, and human or rabbit blood agar are preferred for isolation. After colonies have been scraped aside with a wire loop, pitting of the underlying agar may be evident; alternatively, the colony may leave a small central dot adherent to the agar. Guidelines for the recognition of *C hemolyticum* have been reported by the CDC.[56]

The organism has been consistently sensitive to penicillin, erythromycin and tetracycline. Recurrences have responded to a second course of antibiotics.

Group JK

Although their ecological niche remains unknown, the group JK diphtheroids are probably normal human commensals. Since their description by Hande and colleagues in 1976,[57] the group JK diphtheroids have emerged as important pathogens in two patient populations: immunocompromised patients and patients with prosthetic heart valves.

More than 100 cases of infections due to group JK in compromised hosts have been reported, generally in men (76 percent) over the age of 16 (95 percent) with hematologic malignancy or undergoing bone marrow transplantation.[57-61] Patients with solid tumors frequently are colonized but infections do not commonly develop.[61] Stamm and co-workers[59] have speculated that the prevalence among older men is due to the higher skin sebum levels (secondary to circulating androgens), which favors the growth of these lipophilic diphtheroids on the skin.

Colonization among 98 oncology patients at two hospitals was 30 percent to 40 percent.[59,60] It has been cultured from 0 percent to 12 percent of normal adults and from 13 percent of patients in an acute care hospital. These values represent low estimates because selective antibiotic media were used for isolation. As it is now known that the resistance of the JK organisms is variable,[9,62] some organisms may have been missed. Colonization was most frequent among older men following a prolonged stay in hospital. Nosocomial acquisition and clustering of cases have been described,[60,61] though up to half of patients in whom colonies have been found may be colonized on admission. Most frequently colonized sites were in the inguinal area (89 percent), rectum (87 percent), axilla (70 percent) and throat (9 percent). Hospital reservoirs apart from colonized patients have not been identified.

Bacteremia, pneumonia and cutaneous infections, particularly at bone marrow biopsy sites, perirectal abscesses, and at hyperalimentation and intravenous catheter sites, were most prevalent. Risk factors for infection included colonization, prolonged granulocytopenia, antibiotic pressure and mucocutaneous defects. Patients with hematologic malignancy or undergoing bone marrow transplantation represented 97 percent of bacteremic patients from four series.[57-59,61]

The organisms produce tiny colonies that may have a metallic sheen after three to four days on blood agar. Biochemical testing may show complete inactivity unless supplemented media and prolonged incubation are used. The CDC have recommended biochemical tests for identification of group JK diphtheroids.[9]

Bacteremic isolates from immunocompromised hosts have been consistently sensitive only to vancomycin. Survival in granulocytopenic patients has been related to use of this antibiotic in addition to replacing intravenous catheters. At the Fred Hutchinson Cancer Research Center in Seattle, the attack rate from 1974 through 1977 ranged from 6 percent to 17 percent of patients per year.[59] At that time a combination of gentamicin, carbenicillin and cephalothin was used as empiric therapy in the febrile neutropenic host. Over the past two years at the same institution there was a single

case of bacteremia due to these organisms. During this period a combination of tobramycin, ticarcillin and vancomycin was used for empiric antibiotic therapy. Inclusion of vancomycin in these patients' initial antibiotic regimen may be preventing overgrowth of these organisms on the skin, from which later invasion may occur.

Group JK diphtheroids are probably the most common cause of "diphtheroid" prosthetic valve endocarditis (PVE). Although many reports described infection undoubtedly due to these organisms,[63-65] incomplete speciation was performed on these isolates. There are 26 confirmed cases[62,66-68]; 18 represent all but one of a series of patients with diphtheroid PVE recently reported from Boston.[62] There were infections of 20 prosthetic valves, 4 valvuloplasties, 1 porcine valve and 1 epicardial pacemaker. All had received perioperative antibiotics, the vast majority to which the organisms were resistant. Patients were older (23 to 65 years) but sex was generally not specified. Most cases occurred within the first 60 days postoperatively (73 percent). Identification of the oganisms required approximately six days; in one case the primary isolation was made after 44 days.

Antimicrobial therapy alone was successful only in the absence of congestive heart failure or a paravalvular leak; the presence of either of these conditions necessitated surgical intervention for survival. Myocardial and annular invasion with valve dehiscence was typically seen. Overall survival was 50 percent and was comparable in the medically and surgically managed groups.

These organisms displayed a variable antibiogram. All isolates were sensitive to vancomycin, and most (82 percent to 86 percent) were sensitive to erythromycin, tetracycline and the aminoglycosides. Over 90 percent were resistant to penicillin and the semisynthetic penicillins. Synergy has been shown between vancomycin or penicillin and gentamicin.[62] The addition of rifampin has been advocated, but sensitivity of group JK organisms to rifampin has been variable. The mechanism by which these organisms are multiply antibiotic-resistant is unknown. Organisms tested do not elaborate β-lactamase and plasmids have not been identified by electron microscopy or agarose gel electrophoresis.

It is possible that these organisms play a role in infections in other patients with implanted devices, particularly those with CSF shunts.[41-43]

TABLE 3.—*Nondiphtheriae Corynebacterial Infections in Humans and Their Pathogens*

Endocarditis
Group JK, *Corynebacterium xerosis, Corynebacterium pseudodiphtheriticum, Corynebacterium bovis, Corynebacterium pyogenes*
Pharyngitis
Corynebacterium hemolyticum, Corynebacterium ulcerans
Cutaneous infections
C hemolyticum, C pyogenes, Group JK, *C bovis*
Lymphadenitis
Corynebacterium ovis
Pneumonia
Corynebacterium equi, Group JK, *C xerosis, C ovis*
Central nervous system infections
C bovis, C hemolyticum
Nephritis
C bovis (cerebrospinal fluid shunt)
Compromised host
Group JK, *C equi, C xerosis*

Miscellaneous Corynebacterial Infections

Rare or poorly characterized infections due to *Corynebacterium aquaticum,*[69] *Corynebacterium genitalium,*[70] *Corynebacterium minutissimum,*[71] *Corynebacterium striatum,*[72] *Corynebacterium enzymicum*[73] and various unclassified corynebacteria[74-76] have been reported, and many others have been referred to the CDC.

Concluding Remarks

Infections caused by the nondiphtherial corynebacteria are summarized in Table 3. It is hoped that these reports will stimulate the speciation of all pathogenic diphtheroids. Only in this manner will distinctive clinical syndromes caused by some of these organisms emerge, and we can thus better understand the proper role of diphtheroids in human disease.

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Important Advances in Clinical Medicine

Epitomes of Progress—General and Family Practice

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Gardnerella Vaginitis

RAPID CHANGES have occurred during the past four years in the understanding and treatment of "nonspecific vaginitis." In 1954 Gardner described the role of a short Gram-negative bacillus, then designated as *Haemophilus vaginalis,* in a type of vaginitis that was not due to *Trichomonas, Candida* or *Neisseria.* It was not until 1978, however, when a group of researchers in Seattle reported that this organism may be responsible for virtually all cases of nonspecific vaginitis, that widespread understanding of this condition and the current therapy began to emerge. Recently the organism has been reclassified as *Gardnerella vaginalis.*

The term nonspecific vaginitis is now a misnomer because the clinical picture of gardnerella vaginitis is quite specific. Indeed, as is the case with other forms of vaginitis, this condition may be strongly suspected from the history and findings on physical examination. The characteristic symptoms are a grayish or white discharge and a typical odor. Usually absent are the symptoms of itching, burning or soreness seen with other forms of vaginitis. The odor is described as "fishy," becomes stronger after sexual intercourse and is accentuated by mixing on a slide the discharge with a drop of 10 percent potassium hydroxide solution. This test is diagnostic and may be done in the examination room.

The wet mount preparation in gardnerella vaginitis shows few leukocytes and virtual absence of the normally appearing lactobacilli. Instead there are numerous short bacilli that are barely visible except by a Gram stain under oil magnification. The microscopic confirmation of the diagnosis is usually made of a wet mount by the appearance of the epithelial cells. The cytoplasm of the cells is granulated with the *G vaginalis* organisms and the margins are often indistinct ("clue cells").

Clinicians should be aware that an exact diagnosis in vaginitis may be difficult because of the often simultaneous occurrence of two or more infections.

Gardnerella vaginitis is generally a sexually transmitted disease. Either partner may be an asymptomatic carrier of the organism, so to eradicate the infection both partners should be treated.

Topical therapy has not been effective in treating gardnerella vaginitis. This is particularly true of the topical sulfonamides that have been widely advertised for use in nonspecific vaginitis. At present the treatment of choice is oral administra-

tion of metronidazole (Flagyl). Dosages of 500 mg twice a day for seven days or 250 mg three times a day for seven days for both patient and partner are usually effective. The two-gram single dose that is commonly given for trichomoniasis is not considered sufficient therapy for gardnerella vaginitis. Patients taking metronidazole should be instructed not to consume alcoholic beverages during the treatment period.

There is no effective method available for the treatment of gardnerella vaginitis during pregnancy. The organism is not considered dangerous to the birth process.

Ongoing research will further advance the understanding and treatment of gardnerella vaginitis. Recent studies show that other organisms, particularly anaerobic bacteria, interact with *G vaginalis* to produce the discharge and odor. Researchers in family practice and other disciplines are studying treatment methods and it is hoped that alternatives will soon be available.

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Better Management of Asthma With Mini-Wright Peak Flow Meter

SINCE ARETAEUS first described asthma as "heaviness of the chest; sluggishness to one's accustomed work," the medical definition of asthma has continued to evolve. With the advent of the stethoscope, wheezing was added to the list of signs and symptoms of asthma. In modern times pulmonary function testing has defined asthma on a physiologic basis as "reversible airway obstruction." Evidence of general α-adrenergic hyperresponsiveness in circadian patterns of airway obstruction may allow redefinition of asthma in the future as an abnormality of central nervous system regulation of respiration.

Turner-Warwick has suggested new classifications for asthmatic patients on the basis of patterns of airway "host responsiveness." Using measurements of peak expiratory flow rate (PEFR), she was able to show the recurrence of three predictable patterns of airway obstruction: (1) brittle asthmatic, (2) morning dipper and (3) irreversible. She suggests that the measurement of PEFR to detect these patterns can be used to determine the timing and dose of bronchodilator medications. The PEFR patterns noted by Turner-Warwick may persist from weeks to years and can be modified by appropriately timed treatment guided by home PEFR recordings.

The "brittle asthmatic" condition is characterized by extreme variability of PEFR, analogous to the variability of continuous blood glucose measurements seen in brittle diabetes. The "morning dipper" pattern is characterized by a diurnal pattern of falling PEFR in the early morning. In the irreversible pattern, PEFR measurements over weeks and months reveal minimal diurnal variability, though a modest improvement in mean PEFR may be noted with regular use of bronchodilators or steroids. This pattern is frequently seen in severe chronic obstructive pulmonary disease (COPD).

The Mini-Wright Peak Flow Meter is a simple spring-loaded piston device that measures PEFR in liters per minute during maximal forced expiration. It has a reproducible 98 percent correlation with the standard Wright Peak Flow Meter. The instrument is widely used in Great Britain, and is available through an American distributor for approximately $60. Most patients, including small children, can learn in a few minutes to use the instrument and can make PEFR measurements at home.

Measurement of PEFR in the office, home or work place can be useful in diagnosing and treating airway obstruction. PEFR measurements before and after a challenge with bronchodilator in the office can be used as a diagnostic test for asthma. An increase of 15 percent or more in the PEFR is interpreted as evidence of reversible airway obstruction. Alternatively, a patient may be sent home with the meter to record PEFR four times a day for one or two weeks. Home measurements of PEFR, when correlated with symptoms, may aid in determining optimum timing and dosage of medications. Frequently, optimal dosing can be achieved without the expense of serum theophylline determinations. The need for chronic versus episodic use of bronchodilators may be determined using home PEFR measurements.

In some cases, patients may purchase a Mini-Wright Peak Flow Meter and learn to manipulate their own medication based on a PEFR sliding scale provided by their physician. This self-titration of medication promotes a sense of partnership with the physician and reduces an

illness-associated sense of helplessness in an asthmatic patient. Preliminary experience with the Mini-Wright Peak Flow Meter indicates that selected patients can use this PEFR sliding-scale regimen to improve daily control, resulting in fewer visits for emergency medical care and, perhaps, fewer admissions to hospital.

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Advanced Trauma Life Support

TRAUMA IS SURPASSED only by arteriosclerosis and cancer as the leading cause of death in the United States and is the leading cause of death in the first three decades of life. Primary care physicians are often responsible for the initial care of trauma victims.

Trauma care training previously had been carried out by preceptorship and lectures, neither of which allowed a "hands on" learning experience. Standards for resuscitation of a trauma victim such as those set forth by the American Heart Association for advanced cardiac life support (ACLS) did not exist before 1977. In 1977 a course in advanced trauma life support (ATLS) was developed and revised by the Lincoln Medical Education Foundation, Physicians' Committee on Trauma, Southeast Nebraska Emergency Medical Services, the American College of Surgeons, The University of Nebraska School of Medicine and a number of practicing surgeons. The course was presented statewide in Nebraska to practicing primary care physicians, who were overwhelmingly in favor of the format. As a result, improvement in the condition of severely injured patients was noted.

The ATLS course is quite similar in format to the ACLS course. It is designed for family practitioners and emergency room physicians. There are ten lecture and slide presentations and ten practical skill stations. With these skill stations and lectures, physicians learn various lifesaving techniques, such as chest tube insertion, pericardiocentesis, cricothyroidotomy, peritoneal lavage, application of an antishock garment, application of splints and spinal boards, radiographic interpretation, patient assessment, intravenous catheter placement technique, fluid replacement and endotracheal intubation with an emphasis on nasotracheal intubation. Students must show satisfactory knowledge and technical performance of these skills to their instructor to pass the course. Anesthetized dogs are used for teaching some of the invasive skills. The initial skill assessment station is particularly noteworthy in that it gives students a chance to practice their skills and to be tested on the ability to initially assess and treat a multiply injured patient. Well-coached persons with appropriate simulated injuries are used as patients for students to assess. The students review case histories and appropriate physical findings. The chaos of the typical emergency room is created by the "patients" and the supportive nursing staff. A student must systematically examine a patient, perform lifesaving interventions, order and interpret the appropriate laboratory and x-ray studies in a specified time; otherwise the "patients" will die of their injuries.

Instructor level courses are also available for those interested in teaching ATLS courses. At the University of California, Los Angeles (UCLA), the Family Practice Group has found this training especially useful for physicians in rural sites and an adjunct to ACLS courses for physicians with an active hospital practice. The ATLS course is now available nationally through several groups.

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Preoperative Preparation of Patients

ABOUT 18 YEARS AGO Egbert and co-workers reported that preoperative visits were beneficial in that they gave support and information to patients having elective surgical procedures. The study showed substantial reduction in the use of narcotics, earlier resumption of activities and shortened hospital stays in addition to subjective benefit. Other studies have suggested relaxation techniques taught to patients having an elective operation reduced incisional pain and the need for analgesics postoperatively. Furthermore, informing surgical patients about sensations that will be experienced during the perioperative period effectively reduced stress and the length of hospital stay.

Despite this evidence, routine preoperative

visits by an anesthesiologist or surgeon continue to be mainly perfunctory; rarely is an attempt made by a busy physician to understand a patient's anxieties or to teach simple pain-control techniques. In some hospitals nursing services have taken over this task.

Though program formats vary, efforts are being made to offer all patients this preoperative preparation. At the San Jose Hospital (San Jose, California), for example, the program is run by the recovery room nursing staff to ensure continuity during the early postoperative period. During the early evening before operation an audiovisual program, prepared by the nursing service, is shown to all available preoperative patients. This is followed by a session in which leg and breathing exercises are taught. Each patient is then visited by a nurse who asks open-ended questions (that is, designed to permit spontaneous responses). A summary nursing record sheet is prepared, listing special problems that should be considered during the operative procedure or in the immediate postoperative period. This record includes issues elicited during the interview, such as special fears or anxieties. The summary sheet is reviewed by the nursing staff in the operating room, recovery room and on the surgical floor.

The available evidence is quite convincing that this type of program should be encouraged in all of our hospitals.

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Culdocentesis to Diagnose Ectopic Pregnancy and Pelvic Inflammatory Disease (PID)

PROMPT AND ACCURATE DIAGNOSIS of ectopic pregnancy and acute salpingitis is critical for timely and appropriate treatment. Delay and misdiagnosis can result in an unnecessary surgical procedure, delay in necessary surgical or antibiotic treatment and increased patient morbidity and mortality.

Culdocentesis is a simple, safe and efficient diagnostic tool that allows direct examination of free intraperitoneal fluid and provides immediate, accurate and readily interpretable information. In proved ectopic pregnancy, culdocentesis yields nonclotting blood with up to 82 percent accuracy. Accuracy increases to 97 percent when combined with radioreceptor assay (RRA) pregnancy test. In acute salpingitis purulent peritoneal fluid can be examined directly with greater accuracy than endocervical fluid.

Careful patient selection and good fundamental technique are critical to success. In both suspected ectopic pregnancy and acute salpingitis there should be signs of peritoneal irritation—that is, pain on cervical motion, rebound tenderness, a bulging cul-de-sac or shoulder pain. If a patient has none of these, culdocentesis is less likely to be useful. Similarly, a fixed mass or a fixed retroverted uterus that fills the cul-de-sac contraindicates culdocentesis.

The essential equipment are a speculum, a tenaculum, an 18-gauge spinal needle, a 10-ml syringe (a three-finger control syringe is more convenient), sterile sponges and ring forceps, iodine preparatory solution and gloves. Good sterile technique should be used.

The technique includes the following steps: (1) a thorough pelvic examination, including careful bimanual examination (for cervical tenderness, uterine position, adnexal or cul-de-sac masses or tenderness); (2) speculum placement and preparation of cervix and vagina; (3) application of the tenaculum to the lower lip of the cervix (caution patients about cramps) and positioning of the cervix to allow access to the cul-de-sac; (4) draw 2 to 3 ml of air into the syringe; (5) puncture the vaginal mucosa in the midline 1 cm below its posterior reflection away from the cervix. The needle should penetrate below the cervix and uterus and above the rectum; (6) hold the needle and syringe horizontally and advance 3 to 4 cm through the mucosa; (7) inject the 2 to 3 ml of air. If there is resistance the needle has entered solid tissue and should be repositioned; (8) aspirate, and (9) the procedure is terminated after aspiration of fluid or three dry taps. Bleeding will be minimal.

Complications are very rare and are primarily the result of penetration of pelvic organs, cysts or tumors. They should be avoidable with good technique.

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Diethylstilbestrol (DES) Update 1982

FROM 1940 TO 1971, several million pregnant women in the United States were given a nonsteroidal synthetic estrogen, diethylstilbestrol (DES), most commonly for the prevention of miscarriage. In 1971 Herbst and associates established the link between the development of clear cell adenocarcinoma of the vagina and cervix and DES exposure in utero. Later that year, the Food and Drug Administration (FDA) declared DES contraindicated for use in the prevention of miscarriage. The likelihood of a clear cell adenocarcinoma developing in the vagina or cervix of a DES-exposed daughter now appears to be about 0.14 to 1.4 per thousand. Other abnormalities that may occur in DES-exposed daughters include: vaginal adenosis (columnar epithelium in the vagina), cervical ectropion or eversion and vaginal and cervical ridges that have been described as "collars," "cockscombs," "hoods" and pseudopolyps. These noncancerous abnormalities are present in the vagina of about a third and in the cervix of nearly all DES-exposed daughters.

We are becoming increasingly aware of DES-related problems in pregnancy as DES-exposed daughters reach reproductive age. These women are at significantly increased risk for stillbirth, neonatal death, miscarriage, and ectopic pregnancy as well as for preterm delivery. DES exposure has been implicated in incompetent cervices and abnormally shaped uterine cavities. Pregnant DES-exposed daughters should therefore be treated as high risk patients.

Identification of the DES-exposed daughter is difficult because many are unaware of their exposure. Questions aimed at eliciting a history of DES exposure should be routinely asked of all women born between 1940 and 1971. Evaluation and management for DES exposure should be made according to recommended guidelines: when a female patient with a known history of DES exposure in utero reaches menarche or is 14 years or older, whichever comes first; when any of the abnormalities described above are detected on physical examination, or when a premenarchal girl presents with unexplained vaginal bleeding, spotting or discharge.

Data on DES-exposed sons are less extensive; however, they do show a significantly higher than expected incidence of undescended testes, epididymal cysts, hypoplastic testes, microphallus, lower sperm counts and abnormal sperm. DES-exposed sons should be informed of their exposure when known, and care should be tailored to specific problems.

Because of the anxiety, frustration, guilt and anger experienced by many DES-exposed persons and their families, health care providers must be open, candid and supportive with these patients. For DES-exposed daughters, especially, clear and complete explanations of the DES examination, detected abnormalities, treatment and expectations may be supplemented by referrals to local DES peer-counseling groups.

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Menstrual Extraction

SINCE THE HISTORIC Supreme Court decision in Roe vs Wade in 1973 that removed nearly all legal strictures against abortion, the demand for legal abortion has steadily increased in the United States. In response to this demand, newer and safer procedures for pregnancy termination have evolved. One of the most important of these is menstrual extraction.

Menstrual extraction is an office procedure that can be readily mastered by physicians providing family planning services to their patients. The procedure is somewhat analogous to the insertion of an intrauterine device in that, without prior cervical dilatation, a soft plastic cannula is inserted in the uterine cavity. Instead of using the cannula as a conduit for placing an intrauterine device in the uterus, however, a 50-ml Karman syringe is connected to the cannula and the products of conception are aspirated out. Following the procedure, Rh_0 (D) immune globulin (human) micro-dose (MICRhoGAM) is administered to Rh-negative women to prevent sensitization.

Candidates for menstrual extraction are women with pregnancies less than seven weeks in size and duration from their last menstrual period. The presence of acute pelvic inflammatory disease is the only major contraindication.

Successful termination of pregnancy is possible in up to 99 percent of cases. Major advantages

of menstrual extraction are its lack of serious complications and the fact that it obviates the need for the more expensive and risky dilatation and suction curettage. Immediate side effects occur in approximately 6 percent of patients, and these include syncope, nausea and pain. Late complications include endometritis in 0.8 percent to 2 percent, excessive bleeding in 0.6 percent to 3 percent, cervical or uterine perforation in less than 0.01 percent and incomplete evacuation in 0.6 percent to 2.5 percent.

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Tetracycline for the Treatment of Gonococcal and Nongonococcal Urethritis

IN 1979 THE Centers for Disease Control (CDC) changed the previous recommendation of procaine penicillin as the drug of choice in uncomplicated gonorrhea to include three drug regimens of choice:

- Aqueous procaine penicillin G (APPG): 4.8 million units injected intramuscularly at two sites, with 1 gram of probenecid by mouth;

or

- Tetracycline hydrochloride: 0.5 grams by mouth four times a day for five days (total dosage 10.0 grams). Other tetracyclines are not more effective than tetracycline hydrochloride. All tetracyclines are ineffective as a single-dose therapy;

or

- Ampicillin or amoxicillin: ampicillin, 3.5 grams, or amoxicillin, 3.0 grams, either with 1 gram of probenecid by mouth.

Gonorrhea continues to be a major public health problem, with nongonococcal urethritis (NGU) becoming even more prevalent. Of great concern is the fact that postgonococcal urethritis (PGU) occurs in 30 percent to 60 percent of heterosexual men who are treated with drugs other than tetracycline for their gonorrhea.

Both NGU and PGU are caused by *Chlamydia* or other similar tetracycline-sensitive agents; PGU is simply the infection unmasked after concomitant gonorrhea-chlamydial exposure is treated with a drug that is not effective against NGU. NGU requires at least seven days of tetracycline therapy —0.5 grams by mouth four times a day—and many practitioners therefore treat gonorrhea with tetracycline for this length of time to provide adequate therapy for possible concomitant NGU.

There are other advantages to using tetracycline: (1) like penicillin, it is likely to be effective against incubating syphilis; (2) it may reduce the recent increasing incidence of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains; (3) it was effective against a recently reported case of a gonorrhea strain resistant to both penicillin and spectinomycin; (4) cost, and (5) low incidence of adverse reactions.

Tetracycline should not be used in children, pregnant women or in patients where compliance is an important consideration. Although NGU is not reportable in many states, it should be remembered that, like gonorrhea, the asymptomatic partner should be treated. Tetracycline is an excellent choice for this indication as well.

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Sports Medicine—Objectives of the Preparticipation Evaluation

INCREASING NUMBERS of family physicians are being called on to assess the fitness of potential young athletes to participate in competitive sports. Whereas in the past this assessment was a cursory examination that most practitioners conducted with little thought or preparation, recent evidence suggests that a thorough and rigorous evaluation will benefit both the physician and athlete if the following objectives are accomplished: (1) determination of the general state of health and treatment of remedial conditions; (2) determination of the level of physical fitness and recommendations for same; (3) assessment of size and maturation to aid in determining the safety of participating with peers; (4) evaluation of preexisting injuries and recommendations for rehabilitation where appropriate; (5) restriction of activity or disqualification from specific sports when contraindicated by physical limitations or disease that would preclude safe participation, and (6) recom-

Therapeutic Issues in Turner's Syndrome

In 1938 Henry Turner described seven phenotypic female patients with short stature, sexual infantilism, webbed neck and cubitus valgus. This disorder is now known as the syndrome of gonadal dysgenesis or Turner's syndrome. Over the past 44 years advances in our knowledge of this syndrome and its variants have increased our understanding of normal sexual differentiation and hypothalamic-pituitary-gonadal function during childhood and adolescence.[1] In this issue of the journal, Dr. Hall and her co-workers have informatively reviewed the current state of knowledge of this fascinating heterogeneous syndrome. Despite much progress optimal therapy for the two cardinal features, short stature and sexual infantilism, remains controversial.

Patients with Turner's syndrome are usually small at birth when compared with newborns of comparable gestational age. The pattern of growth in patients with the typical 45,X karyotype is similar; it is influenced by variations in the karyotype (including sex chromosome mosaicism or a structural abnormality of the X or Y chromosome)[1] and by the height of the parents. Patients with Turner's syndrome tend to grow slowly as childhood advances and by 5 years of age are invariably more than 2.5 standard deviations below the mean height for age.[2] The mean final height in 45,X patients is 142 cm with a range of 133 to 153 cm.[2,3] The short stature in patients with this syndrome cannot be attributed to a deficiency of growth hormone, somatomedin or sex steroid hormones of gonadal or adrenal origin. The reason for the progressive growth failure is not known; a diminished response of chondrocytes to somatomedins or other growth factors is an attractive hypothesis supported by indirect evidence.

The use of androgens and so-called anabolic steroids to augment height is controversial and appears to have no more than a modest effect, if any, on final height.[3-5]

Using a different approach we examined bone age and linear growth during "early"- and "low"-dose estrogen therapy in a group of 12 patients with Turner's syndrome.[6] The patients were started on therapy with 0.3 mg of conjugated estrogens at a mean age of 13.6 years. The administration of 0.3 mg of conjugated estrogens was associated with an increase in mean growth velocity from 2.2 to 6.2 cm per year. As with androgens, however, the accelerated growth rate was not sustained. The final height in these patients was not significantly different from that either of patients treated with androgen or of untreated controls.[3,6]

Willemse[7] described the case of a typical patient with Turner's syndrome in whom acromegaly developed. The woman's epiphyses were not fused and she grew from 139 to 154 cm between 18 and 29 years of age. Growth hormone administration in doses used for growth hormone-deficient patients, both with and without anabolic steroids, has resulted in a modest increase in growth velocity in a small number of patients with Turner's syndrome.[5] A study sponsored by the National Pituitary Agency is now in progress to ascertain whether growth hormone in larger doses than those used in the therapy of growth hormone-deficient patients might be efficacious in the treatment of short stature associated with Turner's syndrome. Aside from this empirical approach, more information is needed on the biochemical defect at the level of the chondrocyte because at present we do not have either a clear understanding of the causes of the growth retardation or an effective means for significantly augmenting final height in patients with Turner's syndrome.

In the past, estrogen replacement therapy was deferred until after 15 years of age, engendering serious psychologic problems in patients with Turner's syndrome.[8] This practice was based on the assumption that earlier treatment would lead to rapid skeletal maturation and a diminished height. Our studies do not support this concept.[3,6] We routinely initiate replacement therapy at 12 to 13 years of age with 0.3 mg of conjugated estrogens or 5 μg of ethinyl estradiol a day for the first 21 days of each calendar month. This dosage of estrogen elicits a growth spurt without inordinate advancement of skeletal maturation or reduction in final height; in addition, this dose induces the development of secondary sexual characteristics at an age more comparable with that of normal girls, thereby obviating the undesirable psychologic consequences of a prolonged delay in puberty. Current recommendations based on studies done in patients with Turner's syndrome, as well as experience with estrogen replacement therapy in postmenopausal women, suggest that estrogen replacement should be given cyclically at the lowest dose needed to promote normal sexual maturation and facilitate menses.[1,9-11] We have found that most patients can be maintained on 0.6

mg of conjugated estrogen of 10 μg of ethinyl estradiol a day for the first 21 days of each month. In view of the association between long-term unopposed estrogen therapy and endometrial pathology, including carcinoma, we recommend the addition of a progestin (medroxyprogesterone acetate, 5 mg a day) to the estrogen therapy from day 12 through day 21 of each month.[1,9-11]

Many questions about long-term estrogen-progesterone therapy remain to be answered in patients with Turner's syndrome. Prominent among these are, What is the minimal effective dosage of estrogen and progesterone? Which estrogens and progestins are safest for chronic replacement? To what age should replacement continue? Finally, long-term follow-up may shed increased light on the prevalence of and factors that predispose to other associated problems, such as hypertension not caused by coarctation of the aorta, osteopenia, inflammatory bowel disease, rheumatoid arthritis, Hashimoto's thyroiditis and diabetes mellitus.

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Flawed Theories in a Real World

At this writing it appears that another theory, call it social, economic or political, is running up against realities poorly understood by the theorists. This time it is the theory of "supply side economics" that seems not to be working the way its advocates expected, and may or may not ever work at all. This is only one of a long line of social, economic and political theories that have been conceived (often in ivory towers), tried in the real world (often by government fiat) and found to fall far short of the expectations of the proponents. Could it be that there is some fundamental flaw running through many or even all of these theories?

From the perspective of this one physician the flaw might well be a failure to understand that the real world of human society is a social, economic and political system made up of people who in turn have individual natures and function individually and together in ways we call human. Their natures and their human functioning are fundamental and inescapable characteristics of the people who make up the system, and by extension they must be the essential characteristics of the human societal system itself. If this is true, it may explain why many of the social, economic and political theories that are developed and implemented do not work in the real world. The mystery of their failure may be solved when the real world is analyzed and better understood in terms of the human, even biological, society it has to be. Biological science addresses a biological system *as it is,* and shapes and tests its theories on the basis of what is known to be, rather than the opposite—that is, what *is assumed to be* on the basis of one or another conceptual theory. The real world is real indeed, and one cannot help wondering if much social, economic and political theory is not based on unreal, perhaps even unbiological, assumptions, and is thus flawed. If this is so, it may be little wonder that when such theories are tried out in the real world they fall short of the expectations of their proponents, and do not work well or at all.

—MSMW

Calcium Channel Blockers and Cardiovascular Therapeutics

In 1962 not many pharmacologists and clinicians would have thought that the drug verapamil, introduced in that year as a powerful new smooth muscle relaxant and coronary vasodilator, might represent the prototype of a class of compounds that would make a far-reaching impact on the treatment of many cardiocirculatory disorders.[1] Little was known then about the role of the slow-inward calcium channel in cardiac muscle. Selective coronary angiography was in its infancy.

Provocative tests for evaluating vasospastic propensity in rest angina had not been conceived, though Prinzmetal[2] recently had postulated a role for coronary artery constriction as a basis for the so-called variant angina. Myocardial perfusion imaging had not been developed to document clearly that primary decreases in myocardial blood flow could indeed occur in certain types of angina. Moreover, it was not until the early 1970's that His bundle electrocardiography established the reentrant nature of paroxysmal supraventricular tachycardia.[3]

An important advance was made in 1970 by the voltage clamp technique when it was established that the inward depolarizing current in cardiac muscle was separable into two components.[4] The charge carrier for the fast current was established as sodium ions, the influx of which is blocked selectively by tetrodotoxin and local anesthetic agents. For the slow channel the charge carrier was found to be essentially calcium. It was soon discovered that the slow channel, responsible for excitation-contraction coupling in cardiac muscle and in part for the long plateau phase of the cardiac action potential, could be inhibited specifically and selectively by certain metals such as manganese and cobalt but, more important, by the drug verapamil and its methoxy derivative D_{600}.[4] An appreciation of this phenomenon has led to the delineation of a class of drugs ("calcium antagonists") that, while being chemically heterogeneous, share the common properties of blocking the myocardial slow channel and of inhibiting calcium influx in smooth muscle to varying degrees. Such effects are particularly prominent in isolated tissues, but the in vitro effects are modulated to the extent that the profound negative ionotropic actions of this class of agents is all but nullified (except in the case of severely depressed ventricular function) by the potent vasodilator effects acting to reduce ventricular afterload.

In patients calcium antagonists may produce a complex interplay of simultaneous changes in hemodynamic variables and electrophysiologic measurements. The net effects may vary with each compound, with the level of the autonomic tone (some of the agents, such as diltiazem and verapamil, are noncompetitive sympathetic antagonists), with the level of ventricular function and with the presence or absence of myocardial ischemia. Various calcium antagonists differ also with respect to their potentials for producing vasodilation or for blocking atrioventricular (AV) conduction. An appreciation of such pharmacologic differences and similarities provides the rational basis for the expanding role of calcium antagonists in cardiovascular treatment.

In this issue of the journal, Dr. Deedwania discusses the electrophysiologic and hemodynamic actions of calcium antagonists relative to their clinical applications. A glance at the list of main indications for use—cardiac arrhythmias, ischemic myocardial syndromes, hypertension, hypertrophic cardiomyopathies and possibly myocardial preservation—clearly suggests that the overall spectrum of the therapeutic use of calcium antagonists may well rival that of β-adrenoceptor blocking drugs. However, the therapeutic uses of these drugs and of β-antagonists are not mutually exclusive except in certain well-defined clinical situations. It is worth emphasizing that for most clinical indications the fundamental mechanisms underlying the observed salutary effects of calcium antagonists differ from those of β-antagonists. For example, unlike β-antagonists, calcium antagonists are potent coronary vasodilators and a clear rationale exists for their use in vasospastic angina. This is vindicated by clinical studies and experience on the role of these compounds in angina is likely to increase if the observations of Maseri and colleagues[5] are confirmed. They state that Prinzmetal's angina is only one spectrum of vasospastic ischemic myocardial syndromes. However, it is not known how much more effective these agents are compared with the longer acting, newer preparations of nitrates with better bioavailability. In the case of chronic stable angina, an increasing number of reports indicates that in maximally tolerated dosages, β-antagonists and calcium channel blockers have comparable efficacy. However, β-blockers act essentially by reducing myocardial oxygen consumption as indicated by decreases in the heart rate-blood pressure product at rest and with exercise. For a given effect on angina, calcium antagonists cause less reduction of this product, indicating that the overall antianginal effect is only in part related to a reduction in the gross indices of myocardial oxygen consumption. Other factors may mediate their salutary actions in ischemic syndromes.

As indicated by Dr. Deedwania, calcium antagonists, particularly verapamil, will become the drugs of choice in the rapid termination of paroxysmal supraventricular tachycardia.[6] The success rate for this indication may approach 80

percent to 100 percent when verapamil is given appropriately. The mechanism of the termination is an abrupt block of anterograde conduction in the AV node,[7] the weakest limb of the tachycardia circuit. Diltiazem is less effective in this regard and nifedipine not at all, reflecting the varying effects of these compounds on AV nodal conduction and refractoriness. For other clinical indications, however, nifedipine will be the preferred agent when conduction system disease such as the sick sinus syndrome is present.

Not emphasized by Dr. Deedwania is that, as a group, calcium antagonists have little electrophysiologic effect on the ventricular myocardium; thus they are rarely effective in ventricular arrhythmias except when such dysrhythmias arise on the basis of myocardial ischemia, especially in the wake of coronary vasospasm. In this setting, calcium antagonists may well become first-line drugs in contrast to their limited role in nonischemic ventricular tachyarrhythmias. Of interest is that while these agents, either alone or in combination with β-antagonists, are effective in controlling symptoms in patients with hypertrophic cardiomyopathy, they appear to have little effect on cardiac arrhythmias complicating this disorder. It is unknown whether there is a regression of hypertrophy during chronic therapy.

As indicated by Dr. Deedwania, the data are still scant on other disorders such as arterial hypertension, pulmonary hypertension and congestive cardiac failure, which constitute potential clinical indications for calcium antagonists. More definitive studies are needed to delineate their precise therapeutic roles in this regard. However, it is inherently unlikely that these compounds will, or indeed should, be used for the control of congestive cardiac failure in preference to the plethora of safer vasodilator drugs already available, unless further work shows unequivocal advantages in the case of calcium antagonists in this setting. It should also be indicated that in patients with congestive cardiac failure, digitalis glycosides are nearly always used and that the concomitant use of oral calcium antagonists and digoxin has recently been shown to elevate serum digoxin levels by reducing renal clearance of the glycoside.[8] Thus, the chronic use of calcium antagonists in congestive failure must always allow for such a drug interaction that may induce digitalis-toxic cardiac arrhythmias.

One of the appealing features of calcium antagonists is that as a class of compounds they do not aggravate bronchospasm or interfere with carbohydrate metabolism, nor do they worsen the symptoms of peripheral arterial insufficiency. Indeed, they may even exert a beneficial effect in Raynaud's phenomenon. In these respects, for patients who have such associated complications and yet need treatment with β-blocking drugs for arrhythmias, hypertension, idiopathic hypertrophic subaortic stenosis (IHSS) and ischemic myocardial syndromes, the introduction of orally administered calcium antagonists in the United States is undoubtedly a significant therapeutic advance because their overall spectrum of clinical effects is very similar to those of β-antagonists.

In the case of β-antagonists, there is increasing evidence that the incidence of sudden cardiac death can be reduced significantly by the chronic prophylactic treatment of the survivors of acute myocardial infarction.[9] There is little to suggest that such a beneficial effect is mediated through a direct influence on arrhythmias; the presumption is that the primary action is on ischemia with a secondary effect on electrical instability.

Calcium antagonists are potent antianginal drugs with the additional propensity for reversing coronary vasospasm; like β-blockers, they exert a protective effect on the ischemic myocardium. The question therefore has arisen whether they may also reduce the incidence of sudden cardiac death in the survivors of acute myocardial infarction and in other subsets of patients with ischemic heart disease. A decisive answer to this question is likely to be of far-reaching importance with regard to the expanding role of calcium antagonists in cardiovascular therapeutics.

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CASE REPORTS

Refer to: Brant-Zawadzki M, Wofsy CB, Schechter G: CT evidence of subarachnoid hemorrhage due to presumed 'nathostomiasis. West J Med 1982 Jul; 137:65-67

CT Evidence of Subarachnoid Hemorrhage Due to Presumed Gnathostomiasis

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SPONTANEOUS SUBARACHNOID HEMORRHAGE is due to aneurysmal rupture in most cases and is easily detected with computerized tomography (CT). Nevertheless, approximately 20 percent of cases of subarachnoid hemorrhage documented with lumbar puncture have no explainable cause on subsequent diagnostic evaluation. Parasitic infestation with *Gnathostoma spinigerum* is a surprisingly frequent cause of subarachnoid hemorrhage in the pediatric and adolescent populations of Indochina.[1,2] The presence of a meningomyeloencephalitis with cerebrospinal fluid (CSF) eosinophilia is a strong clue to the cause in such cases. *Angiostrongylus cantonensis,* another nematode found in the Far East, can produce similar features but has a lesser predilection for the spinal cord and generally causes a less severe infection.[3] In view of the recent influx of Indochinese immigrants to this country, it is important for clinicians to be aware of these entities. We report a case of a patient in whom meningomyeloencephalitis with CSF eosinophilia developed and who suffered a subarachnoid hemorrhage on his arrival in the United States.

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Report of a Case

A 21-year-old Laotian man was in transit to the United States from Thailand when he noticed weakness of both legs. On arrival in San Francisco, he was too weak to deplane and was admitted to the US Public Health Service Hospital. He had symptoms of headache, weakness in both lower extremities and inability to urinate. The history was remarkable for leprosy, diagnosed and treated in Laos. Physicial examination on admission showed normal vital signs and no abnormalities. Neurologic examination showed a normal mental status and profound weakness of both lower extremities with areflexia. Sphincter tone was diminished and Babinski's reflex was positive bilaterally.

Laboratory data showed an eosinophilia (22 percent) with a normal leukocyte count. Analysis of the CSF specimen obtained by lumbar puncture on the second day revealed a glucose level of 24 and a protein level of 228 mg per dl, with 1,200 leukocytes (62 polymorphonuclear cells, 29 eosinophils and 8 lymphocytes). Peripheral nerve conduction studies suggested a proximal degeneration of the plexus root or anterior horn cells. Studies of stool specimens for ova and parasites showed *Clonorchis sinensis, Entamoeba coli,* hookworm and *Strongyloides stercoralis.* VDRL was negative. Thiabendazole therapy was instituted.

During his initial hospital course, a sudden right-sided headache and emesis developed with neck stiffness and facial weakness, followed closely by an altered sensorium. The patient was transferred to San Francisco General Hospital for myelography and CT scanning. He remained afebrile. He again was noted to be profoundly weak, with ankle clonus and absent patellar reflexes. Headache, neck stiffness and lethargy persisted.

Myelogram showed no obvious abnormality. The CT scan showed evidence of subarachnoid blood in the perimesencephalic cistern and fourth ventricle (Figure 1). Lumbar punctures again showed CSF evidence of inflammation, with eosinophilia, protein levels in the 100 to 228 mg per dl range, red cells and xanthochromia. Repeated cultures of a CSF specimen for bacteria, acid-fast bacilli, fungi and viruses were negative. Viral

serologies for poliomyelitis, echovirus, coxsackievirus and influenza were negative. Repeat ova and parasite studies of stool specimens revealed further infection with *Taenia saginata* and *Opisthorchis viverrini*. Mebendazole therapy was instituted.

The patient gradually improved, slowly regaining strength in his lower extremities. Follow-up CT scan showed resolution of the subarachnoid hemorrhage. Specimens of serum and CSF, which were sent to the Centers for Disease Control (CDC) in Atlanta to be examined for serologic evidence of *A cantonensis* infestation, were negative.

Discussion

G spinigerum infestation is widespread throughout Asia. Inadequately cooked food, which harbors the third-stage larvae, is the mode of transmission of the agent to humans. The parasite migrates easily through any soft tissue, including that of the central nervous system. It causes damage to neural tissue and blood vessels because of its excessive activity and spinous body. Radiculomyelitis, radiculoencephalomyelitis and subarachnoid hemorrhage are the common manifestations of central nervous system (CNS) *Gnathostoma* infection. Profound CNS involvement and eosinophilia in CSF specimens are initial clues to the diagnosis. Recovery of the parasite from tissue provides definitive diagnosis.[1-4]

Our patient initially suffered symptoms of a myelitis that then progressed to a more generalized encephalomyelitis. Eosinophilia in peripheral blood and CSF specimens was recorded. Clinical and CT findings supported a diagnosis of subarachnoid hemorrhage. In short, the presentation was typical of gnathostomiasis.[3] No other parasites found in this patient could have produced the symptom complex. No other infectious or vascular cause was reported despite extensive examination. Because tissue specimens (usually obtained at autopsy) are needed to definitely establish the diagnosis of gnathostomiasis, only a strongly presumptive diagnosis can be made in this case. The other parasitic infestation that produces CSF eosinophilia and diffuse CNS involvement is *Angiostrongylus,* for which there was no serologic evidence in this case. Although CSF eosinophilia is common in meningoencephalitis due to *Angiostrongylus,* subarachnoid bleeding is

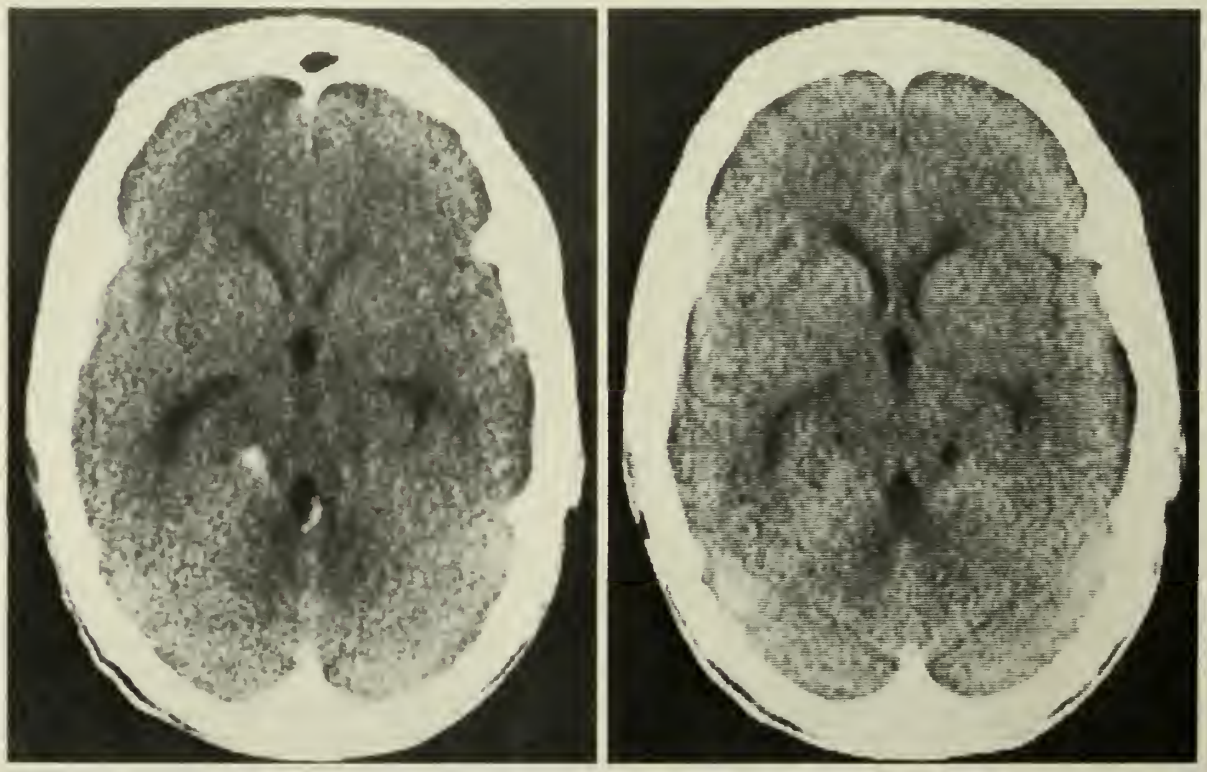

Figure 1—Computerized tomography (CT) scan of 21-year-old Laotian man with gnathostomiasis shows presence of subarachnoid blood in the right ambient cistern and roof of fourth ventricle eight days after the onset of symptoms **(left).** CT scan done one week later shows the clearing of blood from these spaces **(right).**

rare and the tendency for spinal cord involvement much less prominent.[3,4]

CT scanning is quite sensitive for subarachnoid bleeding in the intracranial space. Patients with aneurysmal subarachnoid bleeding generally have hemorrhage detected in the basal cisterns.[5,6] The atypical location of subarachnoid blood on CT scans, in the setting of a Southeast Asian with typical diffuse CNS signs and evidence of inflammation with eosinophilia in the cerebral spinal fluid, should raise the question of *Angiostrongylus* or *Gnathostoma* infestation; the presence of myelitis favors the latter.

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Refer to: Valenta LJ, Eisenberg H, Miller DR, et al: The value of artificial beta cell in the management of insulinoma. West J Med 1982 Jul; 137:67-75

The Value of Artificial Beta Cell in the Management of Insulinoma

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INSULINOMA, a tumor of the pancreatic beta cell causing hypoglycemia, presents a number of diagnostic and therapeutic problems. When use of exogenous insulin can be excluded, a combination of hypoglycemia and inappropriately high serum insulin levels (above 6 to 10 μU per ml) is diagnostic.[1] However, a number of insulinoma patients have fasting euglycemia.

Insulinomas are usually small and difficult to see by radiographic techniques. Even inspection and palpation of the pancreas during surgical procedure may fail to locate the tumor. Occult and multiple lesions are often difficult to find at operation and may require major pancreatic resection, sometimes without relief of symptoms.[2]

This case demonstrates the difficulties of clinical and laboratory diagnosis in a patient with insulinoma, the diagnostic value of subselective angiography and the use of the artificial beta cell in the management of patients.

Report of a Case

The patient is a 26-year-old woman whose principal complaint was periodic loss of consciousness. The first episode occurred at the age of 12 and was preceded by symptoms of catecholamine excess. Later on, episodes of loss of consciousness occurred about every other month and were then introduced by a prodromal period of depersonalization, drowsiness and sometimes generalized jerking movements. The patient said she had no feeling of increased hunger, restlessness, blurred vision, palpitations or any gastrointestinal symptoms. Repeated brain scans and electroencephalograms showed no abnormalities. Nevertheless, a diagnosis of a seizure disorder was made and the patient was started on a regimen of diphenylhydantoin (phenytoin; Dilantin) and phenobarbital, which she had been taking since. There was no relief of the symptoms, and the dosages of phenobarbital and Dilantin were increased progressively. Over the years the frequency of the

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episodes of unconsciousness increased to three to five times a month and their duration up to 24 to 27 hours. There was no relationship of the episodes of unconsciousness to time of day, meals or exercise. Several months before admission, the patient was found to have low fasting serum glucose levels. A prolonged fast was followed by plasma insulin and glucose determinations, with findings consistent with the diagnosis of insulinoma. Subsequently, the patient had an arteriographic examination that included injections of the celiac, splenic and superior mesenteric arteries and was negative both prospectively and retrospectively.

Physical examination on admission showed a well-developed woman whose height was 162 cm (64 in), weight 65 kg (143 lb) and blood pressure 100/60 mm of mercury. She was well oriented and alert, but showed some loss of recent memory. Otherwise her physical examination, including neurologic findings, was completely normal. Biochemical and radiologic studies confirmed a diagnosis of insulinoma as described in the "Results" section.

Methods

Prolonged Fast

Fasting was continued after an overnight 12-hour fast and serum glucose, immunoreactive insulin, C-peptide and cortisol levels were measured every hour.

Glucose Tolerance Test (GTT)

After an overnight fast serum glucose, insulin, C-peptide, cortisol, growth hormone and plasma glucagon levels were measured before and after oral administration of 100 grams of glucose. Blood specimens were obtained at 30 minutes and every hour after the meal for a total of six hours.

Glucagon Test

After an overnight fast 1 mg of glucagon was given as an intravenous bolus. Serum glucose and insulin levels were measured before glucagon administration and 5, 10, 20, 30, 60, 90 and 120 minutes after.

Tolbutamide Test

After an overnight fast the patient received 1 gram of sodium tolbutamide diluted in 10 ml of saline and given intravenously over two minutes. Serum glucose, insulin, C-peptide and cortisol levels were measured before the injection and 5, 10, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after the injection.

Hormone Assays

All hormone measurements were done by specific radioimmunoassays (RIA) using double antibody precipitation.[3] Blood specimens for glucagon were collected in ethylenediaminetetraacetate (EDTA) tubes chilled on ice, the plasma was separated immediately in a refrigerated centrifuge, transferred into tubes containing trasylol and frozen.

The serum immunoreactive insulin was measured directly in the insulin immunoassay. An aliquot of serum was then gel filtered (Biogel P-30) to separate the proinsulin and insulin components and each column fraction was assayed in the insulin radioimmunoassay. The early eluting peak, representing the proinsulinlike component, was read off both the human proinsulin standard curve and the human insulin standard curve. The second peak, representing the insulin component, was measured against the insulin standard. The sum of the individual fractions in each peak is the proinsulin and insulin concentration, respectively. The relationship between proinsulin and insulin is expressed as percentage proinsulin, where both peptides have been calculated from the insulin standard.[4]

Pancreatic Angiography

Subselective pancreatic angiography with a highly concentrated bolus injection of contrast media (10 ml per second) and rapid sequence magnification radiography were used to detect the tumor by looking for a pancreatic parenchymal capillary blush and persistent staining. This technique was previously shown to be successful in the detection of pancreatic endocrine tumors.[5,6]

The Use of the Artificial Beta Cell

A glucose-controlled insulin infusion system (GCIIS) (Biostator®, produced by Miles Laboratories, Elkhart, Ind), was used to monitor and regulate the patient's blood glucose during the surgical procedure. Details of its operation have been described elsewhere.[7] In brief the GCIIS is a glucose sensor linked via a computer to an infusion system that allows either insulin, dextrose or both to be given as needed to maintain blood glucose level within a preselected range. A minute-by-minute record is printed of the mean whole blood glucose level, the dextrose and insulin in-

fusion rates for the subsequent minute and the cumulative insulin dose. In the present studies, the basal dextrose level control constant (BD) was set at 80 mg per dl and the rate of dextrose solution infusion (RD) at 40 mg a minute. Thus, the instrument delivered 40 mg a minute of dextrose if the preceding minute's mean blood glucose level was determined to be 80 mg per dl. Serum glucose sensitivity constant (QD) was set at 20, allowing a relatively sensitive response to a change in glucose level away from 80 mg per dl. The double lumen catheter withdrawal system functioned well without interruption.

Morphologic Studies

Perioperative histologic examination was done by a routine technique on frozen sections of the tissue specimen. As for definitive morphologic studies, the tumor tissue specimen was prepared in three different ways. A portion was fixed immediately on tumor extirpation in 10 percent neutral buffered formaldehyde and prepared for paraffin sections, which were stained with hematoxylin and eosin and indirect aldehyde fuchsin. A second portion was cut into 1 by 1 mm blocks, fixed immediately in 0.1 mol per liter of sodium cacodylate-buffered 2 percent glutaraldehyde for eight hours, rinsed in the cacodylate buffer, postfixed in 1.5 percent osmium tetroxide and embedded in epon resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined by electron microscopy. A third portion of the tumor specimen was freshly frozen and sections of 10 to 15 μm were prepared in a cryostat and stained for immunoreactive insulin by indirect fluorescence. This was done by incubating the slices with an antiinsulin antibody prepared in guinea pigs. After a rinse the tissue slices were exposed to fluorescein-conjugated rabbit anti-guinea pig IgG antibody.

TABLE 1.—*Laboratory Results During Prolonged Fast*

Period of Fasting (hours)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Cortisol (μg/dl)*
12	59	12.5	2.4	18.4
13	55	7.5	2.5	22.4
15	58	6.4	2.3	15.6
16	38	6.6	2.8	13.4
17	28	7.9	2.5	22.0
18	27	6.8	2.6	15.6

The test was performed twice with comparable results. Serum immunoreactive (IR) insulin and C-peptide levels are inappropriately high for the degree of hypoglycemia. There is no increase in serum cortisol in response to hypoglycemia.

Results

Prolonged Fast

After a total of 18 hours of fasting, the patient's speech became slurred, she became drowsy and suddenly lost consciousness. The coma promptly subsided with an infusion of 50 percent glucose solution. The patient did not show any clinical signs of catecholamine excess. Serum glucose level at the time of the coma was 27 mg per dl while immunoreactive insulin level was 6.8 μU per ml. There was no increase in serum cortisol level and the level of serum C-peptide did not change significantly (Table 1).

Glucose Tolerance Test

The patient had slight glucose intolerance with postprandial hyperglycemia persisting at two hours of the test (Table 2). Her serum glucose level later progressively fell to 53 mg per dl. The usual rebound of serum glucose level toward pretreatment value did not occur. The rise in immunoreactive insulin and C-peptide levels was within low normal range. Changes in the serum cortisol level were paradoxical, being elevated during the hyperglycemic phase and suppressed during the

TABLE 2.—*Glucose Tolerance Test Results*

Time (hours)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Cortisol (μg/dl)*	*Plasma Glucagon (pg/ml)*	*Serum Growth Hormone (ng/ml)*
0	65	11	1.9	28.8	24	<0.75
½	125	21	2.9	34.4	<20	<0.75
1	182	27	3.1	31.2	<20	<0.75
2	190	49	3.2	20.8	<20	2.2
3	89	11	1.3	14.4	<20	1.4
4	62	14	2.0	18.8	<20	1.8
5	53	7	2.4	13.6	<20	3.7
6	52	10	0.9	10.4	<20	3.0

Glucose (100 grams by mouth) was given after the 0-hr blood specimen was drawn. The test shows glucose intolerance, serum glucose being elevated to 190 mg/dl at 2 hrs of the test. The response of the immunoreactive (IR) insulin and C-peptide levels is within the low normal range. Insulin response is incompletely suppressed by postprandial hypoglycemia. The response of cortisol is paradoxical. Plasma glucagon level does not rise during hypoglycemia and the response of growth hormone is blunted.

late postprandial phase. Except for the fasting determination, the plasma glucagon level was unmeasurable. The expected response of glucagon is suppression during the hyperglycemic phase and elevation during the postprandial hypoglycemic phase. Serum growth hormone level rose during the late postprandial phase, which is normal, but the response was blunted. Slight glucose intolerance persisted even shortly after surgical removal of the insulinoma.

Glucagon Test

The insulin response to an intravenous injection of 1 mg of glucagon was a rise only to low normal (Table 3). Serum glucose level rose to that seen in normal persons.

Tolbutamide Test

Following infusion of sodium tolbutamide, the serum insulin level promptly rose and then slowly fell to a value of 11 μU per ml at 150 and 180 minutes. A parallel change in the serum C-peptide level was observed (Table 4). Serum glucose value progressively fell and remained in the hypoglycemic range. The test was repeated after successful resection of the tumor. At that time, temporary decline in serum glucose level was followed by a rebound to pretreatment values and the decline of serum insulin and C-peptide levels after a temporary rise was faster and more significant, as seen in normal situations (Table 4).

TABLE 3.—*Glucagon Test Results*

Time (minutes)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*
0	81	7.5
5	98	9.4
10	95	12.0
20	144	14.0
30	149	12.0
60	86	7.1
90	72	5.6
120	53	6.1

One milligram of glucagon was injected intravenously after the first blood specimen was drawn. Serum glucose level rose after glucagon injection due to mobilization of hepatic glucagon and stimulation of gluconeogenesis. However, insulin response was blunted and serum glucose value became subnormal during late phase of the test. IR = immunoreactive.

Serum Proinsulin

The fasting values were as follows: serum glucose 68 mg per dl and direct serum immunoreactive insulin 25.7 μU per ml; proinsulin on the insulin standard was 6.7 μU per ml and insulin on the insulin standard was 17.0 μU per ml. The percentage contributed by proinsulin was 6.7:23.7 or 28.4 percent. When proinsulin was calculated from the proinsulin standard, its value was 1.2 ng (31.3 μU per ml). Postprandially, the respective values were 196 mg per dl (glucose), 61.2 μU per ml (direct insulin), 16.4 μU per ml (proinsulin) and 46.3 μU per ml (insulin). The percentage contributed by the proinsulin was 16.4: 62.7 or 26.2 percent. Thus, both fasting and postprandial concentrations of proinsulin were elevated. Our normal values are between 5 percent and 22 percent.

Angiographic Studies

Because previous routine abdominal arteriography studies using injection of the celiac and superior mesenteric arteries were negative, the

TABLE 4.—*Results of the Tolbutamide Test Before and After Resection of Insulinoma*

	Before Resection			*Two Weeks After Resection*		
Time (minutes)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*
0	48	9.7	4.6	82	4.5	1.8
5	44	27.0	5.2	83	37.0	4.5
10	47	21.0	5.7	..	....	...
15	..	..	..	92	8.4	2.3
20	35	20.0	5.6	..	....	...
30	32	13.0	4.9	49	9.9	3.7
45	39	15.0	4.4	..	....	...
60	39	13.0	3.9	65	7.3	2.5
90	39	14.0	4.0	75	6.9	2.3
120	37	13.0	3.3	77	5.1	1.8
150	39	11.0	2.8	78	6.4	1.8
180	36	11.0	3.8	..	....	...

One gram of tolbutamide was injected intravenously after the first blood specimen was drawn. The normal response of serum immunoreactive (IR) insulin to tolbutamide is an increase to more than 35 μU per ml. The response in this patient before resection was blunted. During the late phase of the test, serum insulin levels were inappropriately high for the degree of hypoglycemia and there was no rebound of serum glucose to normal. After resection of the tumor, the serum insulin response to tolbutamide became normal and there was also a normal rebound of serum glucose to euglycemic level.

patient underwent subselective pancreatic angiography. A highly concentrated bolus injection of contrast material into the dorsal pancreatic artery permitted the complete arterial system of the pancreas to be seen, with reflux into the splenic and hepatic arteries, producing a capillary blush appearance to the pancreatic parenchyma and gross acinar architecture. Two persistent stains were seen (Figure 1). One of these (small arrow) was located in the proximal pancreatic tail and the second was located close to the hilum of the spleen. Either of them could represent an insulinoma. The differential diagnostic consideration for the second lesion was an accessory spleen.

Surgical Intervention

Adjacent to the hilum of the spleen was a firm, encapsulated and somewhat irregularly shaped mass about 1.5 cm in diameter. This mass was of the same size and location as the tumor blush seen on the angiogram close to the hilum of the spleen. The lesion was excised. Inspection and palpation of the rest of the pancreas, including the site of the blush in the body of the pancreas, did not reveal any abnormality.

Use of Artificial Beta Cell During Surgical Procedure

The GCIIS was connected to the patient through the basilic vein an hour before the operation began. At that time, the patient's serum glucose level was 42 mg per dl. Dextrose in water was infused rapidly via the GCIIS to bring the serum glucose level up to 80 mg per dl and the infusion was continued to maintain serum glucose stable at that predetermined value. To achieve this goal, between 40 and 100 mg a minute of dextrose solution had to be infused continuously. Within half an hour after removal of the insulinoma, the need for the infused dextrose solution to maintain serum glucose levels at 80 mg per dl progressively decreased until no dextrose was necessary and even slight hyperglycemia developed in the patient (Figure 2).

Morphologic Studies

The tumor removed from the tip of the pancreatic tail was identified as an insulinoma on both perioperative and definitive histologic examinations. With light microscopy it was seen to be composed of uniform cells arranged in glandular formations. Electron microscopy showed poorly granulated cells as seen in Figure 3. Only occasional granules possessed crystalline structures typical of pancreatic beta cells and corresponding to their secretory product containing insulin (see insert, Figure 3). Immunofluorescent staining for

Figure 1.—Late capillary blush phase of the subselective pancreatic arteriography outlining the parenchymal anatomy of the body and tail of the pancreas. Two superimposed well-circumscribed blushes are seen: one in the proximal tail **(small arrow)** and one in the splenic hilum **(large arrow)**. They were interpreted as possible insulinoma and either insulinoma or aberrant spleen, respectively.

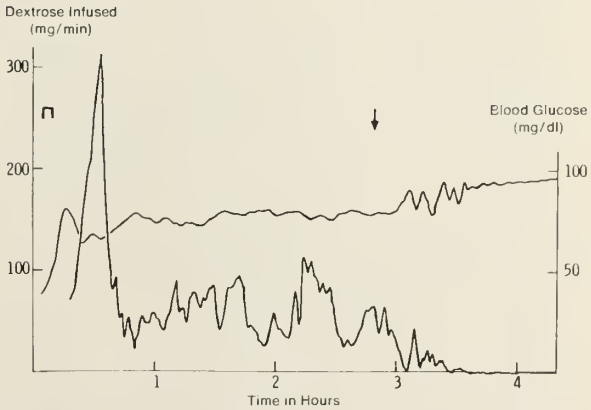

Figure 2.—Use of Biostator during surgical procedure. The upper curve represents blood glucose level as recorded automatically every minute by the Biostator. The lower curve represents the amount of intravenous dextrose infusion in milligrams per minute necessary to maintain blood glucose at a preset value of about 80 mg per dl. The "clamp" corresponds to an intravenous infusion of 5 grams of glucose via Biostator to correct the patient's fasting hypoglycemia. The arrow indicates time at which the insulinoma was removed. Note fluctuations in the dextrose required to maintain euglycemia, possibly reflecting episodic secretion of insulin from the tumor. Removal of the insulinoma was followed about five minutes later by a decreased requirement for dextrose infusion and by upswings and downswings of blood glucose level, which finally settled at about 95 mg per dl, at that time in the absence of any dextrose infusion. These patterns are considered to be typical of successful resection of the tumor.

insulin was strongly positive in the normal pancreatic islet cells. The tumor tissue showed only a slight, diffuse stain (Figure 4).

Discussion

This case report shows the difficulties of diagnosing and treating insulinoma. The misleading diagnosis of a seizure disorder in our patient and the failure to make a correct diagnosis during 14 years of her morbidity may be partially explained by the fact that insulinoma is rare, especially in young people,[1,2] whereas epilepsy is a relatively frequent disorder of childhood. Furthermore, the symptoms of our patient were not clearly related to fasting and exercise. Spontaneous recoveries from coma probably contributed to the confusion.

The cardinal symptom of the disease in our patient was depression of her sensorium, progressing into a coma. Serum glucose levels at the time the patient became unresponsive were as low as between 16 and 27 mg per dl. In the presence of such low glucose concentrations, immunoreactive insulin (IRI) levels in the plasma ranged between 6.8 and 12.5 μU per ml. This was clearly inappropriate for the degree of hypoglycemia and was by itself diagnostic of insulinoma. However, similar values of IRI were also present while the patient was euglycemic (Table 3), so it is difficult to accept that relative hyperinsulinemia alone was responsible for her hypoglycemia. In healthy people in our series, plasma insulin levels in the fasting state are up to 10 to 15 μU per ml in the presence of euglycemia. Because in our patient a higher proportion of the insulin than normal was composed of relatively biologically inert proinsulin, the amount of biologically active insulin in her serum was even lower than measured by the radioimmunoassay.

It is possible that the lack of counterregulatory mechanisms was an important factor in the genesis of hypoglycemia in our patient, in addition to the inappropriate insulin secretion. This was suggested

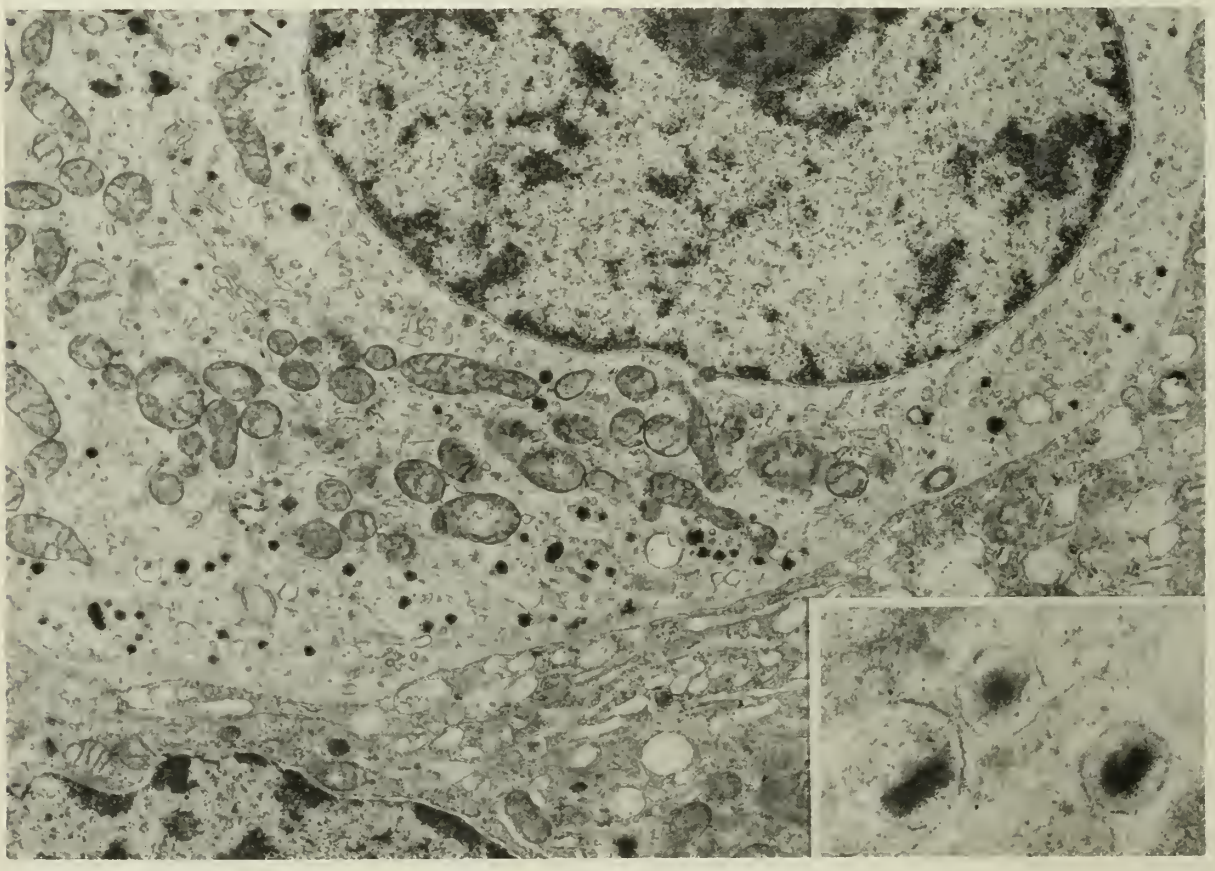

Figure 3.—Electron microscopy of the insulinoma cells (reduced from magnification ×15,680). Parts of two adjacent tumor cells are seen. The cells are rich in mitochondria, smooth endoplasmic reticulum and free ribosomes. Secretory granules can be seen containing mostly amorphous electron-dense contents. Only occasional dense granules contain crystalline structures believed to correspond to insulin (**insert**, reduced from magnification ×89,600). The secretory granules were often associated with well-developed Golgi complexes.

Figure 4.—Indirect immunofluorescence study of the pancreatic tissue using guinea pig antiinsulin antibody and fluorescein-conjugated rabbit antiguinea pig IgG antibody (reduced from magnification ×250). Exocrine pancreas **(dark zone)** does not react. Insulinoma, on the right, has a relatively weak reaction for insulin. Parts of two normal islets can be seen with a strong positive reaction for insulin **(white areas).**

by the following findings: During the hypoglycemic phase of the glucose tolerance test, plasma glucagon determination failed to show increase as expected. Increase in serum cortisol level in response to hypoglycemia was blunted or absent on several occasions: during the prolonged fast, GTT or tolbutamide provocative test. The response of growth hormone to hypoglycemia during GTT was blunted. Although plasma catecholamine levels were not measured, the absence of symptoms of catecholamine excess during episodes of severe hypoglycemia suggested that their secretion was also inadequate.

It is not clear why the response to hypoglycemia of the hormones opposing the excessive anabolic action of insulin should have been inadequate. The counterregulatory hormone secretion may have escaped from dependence on hypoglycemia, as this became a chronic condition. It can also be speculated that the insulinoma produced compound(s) inhibiting the secretion of the counterregulatory hormones. Such substances can be, for example, somatostatin, which is a normal secretory product of the islet cell tissue. An attempt was made to measure plasma somatostatin levels by RIA* in this patient but was unsuccessful due to high nonspecific binding.

Another possibility is that the insulinoma produced insulin that was biologically active but relatively inactive immunologically. Release of other hypoglycemic factors such as nonsuppressible insulinlike activity (NSILA) should also be considered. It is unlikely that the patient would have shown increased sensitivity to insulin. In insulinoma patients, decreased sensitivity to insulin was reported, probably due to decreased self-regulation of insulin receptors in states of chronic hyperinsulinemia.[8]

In normal persons, the serum insulin-glucose ratio decreases during prolonged fast, which is also found in hyperinsulinemic states such as obesity. In contrast, under similar conditions the serum insulin-glucose ratio increases in insulinoma patients.[9] In our patient, some progressive decrease of serum insulin and C-peptide levels also occurred with prolonged fast and the development of hypoglycemia, but the insulin was never lower than 6 μU per ml.

Various ratios between serum glucose and IRI were recommended to be used in diagnosis of insulinoma, such as glucose:IRI, less than 2.5; IRI: glucose, greater than 0.3; 100×IRI divided by (glucose−30), greater than 50. Diagnostic failures were found to occur with all of these ratios.[1] Taking into account values obtained in our patient during prolonged fast, that is, 27 mg per dl for serum glucose and 6.8 μU per ml for serum insulin, the second and third ratios would be diagnostic of insulinoma, but not the first one. The major difficulty in establishing various ratios is the fact that between different laboratories the normal range and sensitivity of the assay for serum glucose is much more standardized than that for serum IRI. Therefore, it is again emphasized that in the presence of significant hypoglycemia, the serum insulin should be undetectable and measurable serum IRI should raise a suspicion of the presence of insulinoma when use of exogenous insulin can be excluded.

Serum insulin and C-peptide responses to provocative stimuli in our patient were within the low normal range. This was true for the oral glucose tolerance test, the glucagon test and the initial phase of the tolbutamide test. The provocative tests did not add anything more convincing to this observation and they should not be used routinely in the diagnosis of insulinoma.

Insulinoma cases have been reported wherein the reaction of insulin to provocative stimuli and to suppression was either normal or absent.[10,11] Glucose intolerance that develops in some of these patients is believed to be a result of atrophy of the normal tissue due to the chronic hyperinsulinemic state. However, atrophy of normal islets is

*Courtesy of Roger H. Unger, MD, Department of Medicine, University of Texas Southwestern Medical School at Dallas and the Dallas Veterans Administration Medical Center.

probably less frequent than suspected. The insulin content in the uninvolved tissue was found to be normal.[12] In our patient, the islets in the tissue beyond insulinoma had a normal histologic appearance and stained strongly for insulin by immunofluorescence. Why, then, the mild glucose intolerance developed in the patient is not clear, but it again raises the possibility of secretion by the tumor of a humoral inhibitor of insulin release from the normal tissue or a decreased peripheral sensitivity to the insulin action. This seems to be supported by the fact that after the surgical procedure the response of IRI to intravenous tolbutamide became normal, whereas before the surgical procedure it was blunted (Table 4).

It is impossible to determine to what extent the insulin response is influenced by normal pancreatic tissue. In some patients at least, insulinoma may release insulin independently of the regulatory mechanisms and any changes in plasma insulin could be due to superimposed secretion of insulin from normal islets.

Determination of serum proinsulin was helpful in the diagnosis of our case. The proportion of proinsulin was elevated in both fasting and stimulated states, as previously demonstrated by others.[13-16] At the electron-microscopic level, the insulinoma cells contained only a few secretory granules with crystalline structure that are believed to correspond to insulin. Most of the granules contained amorphous material, consistent with proinsulin.[17]

Locating and surgically resecting an insulinoma is a prerequisite for the cure of the disease. This can be a difficult task. In a large series of 154 cases of Laroche and co-workers,[2] curative resection of insulinoma was accomplished in only 78 percent. The course of 22 patients in whom no tumor was identified was unfavorable. Perioperative location of the tumor by palpation is frequently unsuccessful in the case of small tumors, and this is critical for successful resection.

In our patient, two techniques proved to be especially helpful to the surgeon in identifying the insulinoma: the preoperative use of subselective pancreatic angiography and the use of artificial beta cell during surgical procedure. Pancreatic angiography directed the surgeon to areas showing a persistent tumor stain, one of which proved to be the insulinoma. It has been shown by one of us (H.E.) previously that this technique can routinely locate tumors under 1 cm in diameter[5] when employing a specific technique that combines high-bolus subselective pancreatic artery injection with high-resolution magnification filming technique. No side effects were observed in more than 100 patients studied. Clinical signs of pancreatitis did not develop in any of the patients and, following the procedure, serum amylase levels remained unchanged. Preoperative location of insulinoma by angiographic techniques has been reported to be successful in between 40 percent to 90+ percent of patients.[18-20] To increase the accuracy of such a procedure, it should be subselective and use subtraction, magnification and stereotactic techniques. Transcutaneous and transhepatic pancreatic venous sampling can locate an insulinoma even more specifically by showing a stepwise gradient of immunoreactive insulin in veins draining the tumor.[18] However, successful selective venous catheterization and specimen sampling remains a difficult procedure accompanied by considerable morbidity.

In our case, the artificial beta cell proved to be extremely helpful during surgical procedure by keeping the patient's serum glucose at a preset euglycemic level through continuous intravenous infusion of a dextrose solution and by indicating the time of successful removal of the insulinoma. Between 5 and 15 minutes after resection of the insulinoma, the requirement for dextrose for maintaining euglycemia gradually decreased until none was required and the serum glucose level became stable at between 95 and 100 mg per dl. In our case, where two lesions were suspected to be present from the angiographic study, it was important to identify the resected tissue as the only critical tumor responsible for hypoglycemia and this made it unnecessary to take a biopsy or resect the area of the second tumor blush. Artificial beta cell has been used previously for the same indications.[21,22] Similar results were obtained showing a rise of serum glucose level shortly after removal of the insulinoma. In cases where no tumor can be identified preoperatively or during surgical operation, sequential resection of the pancreatic tissue in a patient continuously monitored by an artificial beta cell should indicate removal of the tumor.

Summary

We present the case of a 26-year-old woman with a 14-year history of periodic comatose states treated originally as a seizure disorder. A diagnosis of insulinoma was made, mainly on the basis of inappropriately high plasma insulin concentra-

tion (above 6 μU per ml) in the presence of significant hypoglycemia, and elevated proinsulin levels. Routine abdominal angiography studies were negative. Subselective pancreatic angiography showed two areas of persistent tissue stain. One of those proved to be an insulinoma. Surgical treatment was done while the patient was continuously monitored by an artificial beta cell. This was found to be very useful for maintaining the patient's serum glucose level in the euglycemic range and for confirming removal of the insulinoma. To maintain euglycemia, a dextrose solution had to be infused continuously via the artificial beta cell. However, between 5 and 15 minutes after removal of the insulinoma, the need for dextrose infusion gradually decreased to zero and the patient's serum glucose level settled down at 95 to 100 mg per dl. This was regarded as proof of resection of the critical tissue, and thus the second persistent stain observed on subselective angiography was defined as a false-positive finding.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Rising Health Care Costs

To the Editor: May I say "right on" to your reprinted 1968 editorial "Rising Health Care Costs" in the April 1982 issue of the journal?[1]

As providers of medical care, physicians are caught in the middle of a "Catch 22" situation on the issue of health care costs. Let us hope that in time the public will understand that physicians in general provide the best care they can under prevailing circumstances. They do not promise, as the politicians and bureaucrats do, that such care will be available to everyone at negligible cost.

However, there appears to be a faint ray of hope for physicians in California: the astute Speaker of the Californ'a Assembly, Mr. Willie L. Brown, acknowledged recently that, perhaps, the state can't afford "mainstream" care for all its citizens. Now, he and other government officers and officials should acknowledge that it is not the costs of care by physicians alone but also those of all other health carc providers, especially hospitals, and the overall inflation in this country, that are responsible for health care cost increases. Should the foregoing ever occur, then as physicians we can spend less time fighting in the political arena and devote more time in the health field for which we arc trained and needed.

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Another Indication for Coronary Bypass

To the Editor: The April Medical Progress review by Carr, Engler and Ross of the persistent question of prolongation of survival after surgical bypass is a thoughtful and critical assessment of many reports.[1] The editorial comments by Braunwald and Stone[2] add emphasis and an independent perspective. Both deal with the issues on the basis of the clinical history and pertinent data obtained by invasive catheterization studies to define pertinent details of anatomical disease and functional impairment in the patient at rest. *Neither deals with the presenting clinical problem of whether further trials of medical treatment or diagnostic studies for possible surgical treatment should be recommended when a symptomatic patient with angina is first seen.*

It is in this context that it seems appropriate to call attention to still another report from the noninvasive exercise testing unit of the Seattle Heart Watch[3] which was not cited in Carr and co-workers' excellent review. In the Seattle study retrospective analysis of data collected from 1971 through 1975 on 1,670 patients who did not have operations and 331 patients with coronary heart disease who did have operations identified two important pathophysiologic syndromes that had notably different four-year survival rates in relation to nonrandomized choice of medical or surgical treatment. One was exertional myocardial ischemia characterized by chest pain on exercise testing or ischemic ST depression after such exertion (or both); four-year survival rates of 91 percent to 92 percent indicated no difference in these low-risk patients. The other was designated as left ventricular dysfunction based upon any one or more of three findings: cardiomegaly, exercise duration less than three minutes in stage I (Bruce protocol, requiring 4 to 4.5 mets [metabolic units, multiples of the resting oxygen consumption] of energy expenditure) and peak systolic pressure less than 130 mm of mercury during exercise.

Of all the patients who received surgical treatment, unexpectedly 34 percent had this syndrome and achieved a 94 percent survival by four years. In contrast in the patients who did not have operations and were medically treated, all of whom had at least one artery deemed feasible for grafting by the arteriographers, the survival was only 67 percent ($P<.01$) by fours. *These patients could be screened and classified noninvasively by the*

findings on initial clinical examination and exercise testing even in office practice.

Thus, at the initial appraisal, these findings offer useful guidelines to a physician as to whether it is better to proceed with the necessary invasive studies and, if feasible, surgical bypass soon or to evaluate responses to one or another of the available medical regimens first. Clinical experience using these guidelines has been satisfactory to date and, when on subsequent examination and testing of the patient, evidence of left ventricular dysfunction by these criteria emerges, invasive studies and usually a bypass surgical procedure are carried out. This approach, however, does not preclude recommendations for surgical intervention in patients without left ventricular dysfunction when vigorous medical therapy has failed to control symptoms adequately.

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Cheating Beyond Medical School

To the Editor: With reference to the February editorial[1] "Cheating in Medical School," I admire the idealism inherent in the statement that the maturation process will correct the problem addressed in the editorial. I am prompted, however, to share a recent experience with your readers which may belie your optimism.

During my recent attendance at the California Medical Association's annual meeting, I elected to visit the scientific and commercial exhibits. Having five exhibitors sign a small card entitled visitors to a drawing for a portable television set. When I returned to deposit my card, I noted another physician copying signatures from one card to several others. Not being known for shyness, I asked him what he was doing and he responded that he was making copies for his personal files. I next observed him to deposit all of these cards in the basket.

This rampant display of dishonesty by one of my colleagues turned my stomach. I share your view that personal and professional integrity is the "sine qua non" of the confidence placed upon us by our patients and by the public in general. It is the medical ethic, as it were, of which such integrity is but one component, that places our profession in continued high esteem. My experience leads me to doubt the conclusions stated in your editorial. I shudder to think that whereas only a small number of our colleagues behave in such fashion, the numbers may increase in the future. Furthermore, if the physician in question will publicly volunteer his identity, I'd be happy to buy him a TV set.

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REFERENCE

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Bleeding After Liver Biopsy

To the Editor: I read with interest the article by Mahal and co-workers regarding bleeding after liver biopsy.[1] These investigators found that relative contraindications to biopsy were present in 10 of 22 patients studied among those who bled and in only 2 of 41 nonbleeding controls. They conclude that bleeding could have been prevented in at least some of these patients by more careful attention to the contraindications of liver biopsy.

Mahal and his colleagues overlook, however, the remaining 12 patients who bled significantly although they had no apparent contraindications to the procedure. I believe this set of patients is more intriguing than the ten patients who had contraindications because it is already widely acknowledged that liver biopsy should not be carried out if the prothrombin time is prolonged three seconds more than the control and the platelet count is below 80,000 per cu mm.[2,3] However, it is not generally recognized that bleeding after liver biopsy does not correlate with indices of peripheral coagulation.[4] Ewe found, in a prospective study of 200 patients, that "liver bleeding time," which is the time interval between the biopsy and termination of hemorrhage as observed by laparoscope, does not correlate with any of these following variables: prothrombin time, platelet count, whole blood clotting time, length of the biopsy cylinder and liver histology.[4] This is important to note because all too often a normal coagulation profile provides a false sense of security.

In view of Ewe's findings, Mahal's 12 patients who bled after liver biopsy, although no relative

contraindications were present, teach us an important practical detail that the authors do not state: We still have no reliable laboratory test available that can predict hemorrhagic complications after liver biopsy in any individual patient and any relative contraindication remains only empirical.

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Acute Arthritis in the Elderly

To the Editor: In the correspondence section of the January 1982 issue, Robert M. Heiligman, MD, described the case of an elderly woman with intermittent acute pain in the right hip and shoulder.[1] He felt the case fulfilled requirements for "palindromic asymmetric polymyalgia rheumatica."

Dr. Heiligman carefully pointed out that polymyalgia rheumatica has not been felt to be either palindromic or asymmetric in its clinical presentation. As there are no definitive laboratory tests for polymyalgia rheumatica, this remains a diagnosis of exclusion. In the case described by Dr. Heiligman, I would raise another perhaps more likely diagnosis, namely calcium pyrophosphate dihydrate (CPPD) deposition disease. This is a fairly common cause of acute arthritis in the elderly. The patient's history of intermittent asymmetric attacks, elevated erythrocyte sedimentation rate and response to corticosteroids are all consistent with pseudogout. Although not as commonly involved as the fibrocartilage of the knees, wrists and symphysis pubis, the hips and shoulders are not infrequent sites of radiographic chondrocalcinosis and pseudogout attacks.

Dr. Heiligman does not describe any radiographic findings in this patient. I believe that a radiographic survey of the involved joints as well as the knees, pelvis and wrists would be likely to show chondrocalcinosis. Although a definitive diagnosis of pseudogout requires identification of short positively birefringent CPPD crystals in synovial fluid or synovial biopsy, radiographic evidence of cartilage calcification would strongly suggest that clinical diagnosis.

Dr. Heiligman's case points out the often difficult differential diagnosis of acute arthritis in the geriatric population.

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Pulmonary Embolism in Buerger's Disease

To the Editor: In the September 1981 issue, under the title "Recurrent Pulmonary Emboli and Buerger's Disease" there is a report about a patient with Buerger's disease in whom the initial clinical manifestation was an acute pulmonary embolus.[1] The authors in their introductory comments and in their discussion mentioned their inability to find reports of pulmonary vascular involvement in living patients with Buerger's disease. In addition, they stated that to their knowledge Buerger's disease with pulmonary embolization as an initial manifestation had not been reported previously.

A review of the literature on Buerger's disease points up clearly that pulmonary embolism in Buerger's disease is indeed a rare event, a fact that is reiterated in the older literature.[2] Edwards,[3] while pointing out the rarity of the finding, stated he knew of one nonfatal instance of pulmonary embolism in Buerger's disease and, in addition, referred to Kahn's case[4] (which was cited in reference number 8 of the September article). The case of Kahn was that of a Polish soldier with thromboangiitis obliterans, who had an episode of pulmonary infarction of the right lower lobe that was diagnosed during life, and was still living some 14 months after the episode. Murphy[5] reported that in a period of four months he encountered three patients with Buerger's disease in whom pulmonary embolism occurred. Case 1 in Murphy's series was that of a railroad man in whom pulmonary infarction was the initial manifestation of Buerger's disease. Lung infarct was diagnosed in all Murphy's cases during life.

It should be pointed out that one could reasonably question the accuracy of some reports of pulmonary embolism in the older literature because of the nonavailability of the specific diagnostic techniques that are now used in arriving at

a diagnosis of pulmonary embolism. Also, Murphy's criteria for diagnosing Buerger's disease are not clear.

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Traveler's Diarrhea

To the Editor: Emporiatic enteritis (traveler's diarrhea, *turista*, Montezuma's revenge) has been reported in as many as 40 percent of members of groups visiting endemic areas,[1] and has been linked to an enterotoxigenic *Escherichia coli* as one of the etiologic agents.[1] Various modalities for prophylaxis have been recommended to decrease the rate of affliction, but no study has been reported to compare the various efficacies of these therapies.

I recently served as the tour physician for the members of the Los Angeles Philharmonic Orchestra, and distributed a questionnaire to the orchestra four days after completing a six-day tour of Mexico City, soliciting retrospective data about health problems including diarrhea during the preceding ten days. Of 110 questionnaires, 93 (85 percent) were returned. A rigorous health orientation was offered to the orchestra before departure, outlining nonmedicinal precautions to be taken with regard to food and drink. Prophylaxis with doxycycline (200 mg to start and 100 mg every day for the duration of the Mexican portion of the tour[2,3]) and Pepto-Bismol (2 oz four times a day[1] or two tablets four times a day) was made available. The use of *Lactobacillus acidophilus* tablets (freeze-dried) was discussed with more "holistic" members of the orchestra.

Overall, 37 percent of the orchestra had some instances of diarrhea reported, and only 24 percent had it more than four times a day. Thirty-nine people took no prophylactic medication, and they had a 30 percent diarrhea rate. Twenty-four people took doxycycline for prophylaxis, with 16 percent having any diarrhea. Fourteen people reportedly took the *L. acidophilus* tablets prophylactically, with a 42 percent diarrhea rate. Fifteen people took Pepto-Bismol, but it later appeared that the questionnaire was unclear as to that which was taken for prophylaxis versus that taken for therapy, as they had an 80 percent diarrhea rate. Although none of these data are statistically significant, they are suggestive of the usefulness of doxycycline as prophylaxis.

Analysis of the relationship between food and drink and the incidence of diarrhea failed to show much difference between being "compulsively careful" and "moderately careful." It is clear, however, that the large number of people who were at least moderately careful did have less diarrhea than those who were "not at all careful." There was no relation between meals taken only at the hotel, meals taken elsewhere, the use of hotel water *(agua purificada)* for drink or the brushing of teeth, and the incidence of diarrhea. There did not appear to be a relationship between previously having had traveler's diarrhea, having a "sensitive stomach" or the instrument played and the rate of diarrhea. Anxiety about concerts on tour was not a significant factor. No one was unavailable for a concert due to significant illness until the seventh day.

In summary, some lessening of the overall diarrhea rate may have been achieved by a careful predeparture orientation of all members of the orchestra. Those who took doxycycline had less diarrhea than any other group. The *L. acidophilus* tablets may have caused more diarrhea than they prevented. The role of Pepto-Bismol in the prophylaxis of emporiatic enteritis is unclear.

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Birth Parents, Adoptive Parents and Adoptees

To the Editor: I was late in reading my journals, so just recently I noted the letter from a medical student, C. Mark Hynum, in the February 1982 issue[1] in response to our own article of July 1981,[2] "Adoption: Pediatric, Legislative and Social Issues," and the comment in the October 1981 issue by Xavier Gonzalez, MD.[3]

As a belated reply, first to Dr. Gonzalez: The need and the desire for anonymity of the birth parent has been greatly overemphasized. The few

who still feel this way are greatly overbalanced by the majority of birth parents eager to find these children.[4] In fact, many adoptees do not even seek out these parents, but are satisfied with information about their heritage. Persons working in the adoptive field use the term birth parents to distinguish this person (or persons) from the adoptive parents who are the true psychological and meaningful parents of the adoptee. Much of this was eloquently expressed in the reply by C. Mark Hynum in the February 1982 issue.[1] As an adoptee, he understands many of the problems of which much of the medical profession is unaware. Only recently has adoption come out of the closet and people in the adoption community are becoming able to express their feelings and their problems.

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Western Student Medical Research Forum

To the Editor: There is concern among medical educators that diminishing student interest in academia as a career threatens the quality of future medical education and the vitality of American clinical research.

It is said that among previous generations of medical students, about half expressed interest in academic careers, while today only a few are so inclined. The reasons for this are complex and include economic as well as other factors.

Measures currently being taken to counter this trend include increases in clinical investigator traineeship positions and support for medical student research.

One of the most vigorous and, I believe, successful efforts to encourage student research is being coordinated by a lay person. The Western Student Medical Research Forum (WSMRF) provides an opportunity for students to present their work in a scientific session held conjointly with the Annual Meeting of the Western Section of the American Federation for Clinical Research (AFCR). Representing the 16 western medical schools, the WSMRF has earned a remarkable reputation for quality and consistency among student research forums.

Since 1974 the WSMRF has been coordinated by Mrs. D. P. Bertakis of Sacramento, California. She became involved when her daughter, then a student, became chairman of the Forum. Mrs. Bertakis realized the need for expert administrative direction if this student-initiated effort was to thrive.

And thrive it did. The 1982 Forum saw more than 60 student papers presented, and had noted faculty representation throughout its two-day program.

Mrs. Bertakis has made a truly commendable contribution to medical education. Without remuneration, she annually spends considerable time organizing what may be the gem of medical student research forums. She has touched the lives and, I believe, influenced the career direction of medical students throughout the West. In addition, she may have shown us a particularly effective way to rekindle student interest in academia as a career.

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Heparin-Induced Thrombocytopenia

To the Editor: The article entitled "Risk of Complications During Intravenous Heparin Therapy"[1] by Nelson and co-workers in the March issue was well-written and informative. Unfortunately, the character of their series underestimates the incidence of heparin-induced thrombocytopenia (HIT) as a risk of heparin therapy, and their conclusions underemphasize its significance. Heparin-induced thrombocytopenia is a major complication of heparin therapy. In susceptible persons an immunologically mediated response causes increased platelet adhesiveness and aggregation.[2] Platelet-fibrin clot formation may follow, causing arterial or venous thromboembolism. Both large and small vessels may be occluded, including the abdominal aorta, sagittal sinus and coronary arteries. Clinical manifestations include limb ischemia, recurrent venous thrombosis, myocardial infarction and cerebrovascular accidents. When associated with arterial thromboembolism, the mortality of this complication may be as high as 60 percent.[3]

Heparin-induced thrombocytopenia is not limited to that population that Nelson and associates found to be most at risk for heparin complications

—that is, those above the age of 60 and those with concurrent disease. In 1977 we reported on three patients with heparin-induced thrombocytopenia.[4] None had concurrent disease, and their ages were 75, 49 and 31 years. The 31-year-old patient, receiving heparin therapy for a pulmonary embolism, had a thrombosis of the abdominal aorta with subsequent permanent paraparesis and ischemia of one leg requiring an above-the-knee amputation. The incidence of HIT reported in the literature varies widely. Although one prospective study showed an incidence of 31 percent,[5] most authors feel the true incidence is significantly lower than this figure. Nelson and coauthors admit that the incidence they report (1.5 percent) may be falsely low due to the lack of frequent platelet count determinations in their patients. However, in assessing the reported incidence of HIT, one must consider not only the frequency of platelet count determination but also the duration of heparin therapy. HIT occurs between 2 and 14 days after the onset of treatment.[5] Thus, only 107 of Nelson's patients may have been expected to be susceptible to this complication.

Although of low incidence, HIT may occur in any patient, including those of young age and without concurrent disease. Respecting the significant morbidity and mortality of this complication, we strongly recommend daily platelet count determination for all patients receiving heparin therapy.

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REFERENCES

1. Nelson PH, Moser KM, Stoner C, et al: Risk of complications during intravenous heparin therapy. West J Med 1982 Mar; 136:189-197
2. Fratantoni JC, Pollet R, Gralnick HR: Heparin-induced thrombocytopenia: Confirmation of diagnosis with in vitro methods. Blood 1975; 45:395-401
3. Weismann RE, Tobin RW: Arterial embolism occurring during systemic heparin therapy. Arch Surg 1958; 76:219-227
4. Baird RA, Convery FR: Arterial thromboembolism in patients receiving systemic heparin therapy: A complication associated with heparin-induced thrombocytopenia. J Bone Joint Surg [Am] 1977 Dec; 59(8):1061-1064
5. Bell WR, Tomasulo PA, Alving BM, et al: Thrombocytopenia occurring during the administration of heparin—A prospective study in 52 patients. Ann Intern Med 1976 Aug; 85:155-160

* * *

TO THE EDITOR: An important finding in the study by Nelson and co-workers[1] that deserves greater emphasis is that bleeding complications during heparin therapy do occur even when only modest doses of heparin are employed. It is sometimes argued that close monitoring or various in vitro coagulation tests will help prevent bleeding complications, presumably by avoiding excessive anticoagulation. What were the activated partial thromboplastin time (PTT) values in the patients who bled?

We reviewed the records of 121 patients with objectively documented deep vein thrombosis treated by continuous heparin infusion. Eleven patients (15 percent) had significant bleeding complications. The activated clotting time (ACT) was in the therapeutic range (150 to 190 seconds) in 9 of the 11, less than 150 seconds in 1 and greater than 190 seconds in the other. Of the 121 patients, 26 received "high dose" heparin therapy (150 units per kg of body weight and 30 to 40 units per kg of body weight per hour without regard to ACT levels) and the remainder, 95, received more conventional doses (50 units per kg bolus with subsequent infusion rates adjusted to achieve a therapeutic ACT). Significant bleeding occurred in 2 of 26 high-dose heparin cases and 9 of 95 conventional dose cases, an insignificant difference. The high-dose group had no recurrent thromboembolism whereas in the conventional-dose group there were eight documented cases of pulmonary embolism ($P = .047$), one of which was fatal.

Another point that deserves mention is the exercise of questionable judgment in giving heparin to patients with a high risk of intracranial bleeding. Few would argue against withholding heparin therapy in this group of patients. The judgment that must be made in each case is whether the risk of heparin therapy outweighs the risk of further thromboembolism. In most patients, as the authors have concluded, the risk of heparin therapy is minimal. In others, avoiding anticoagulation and employing vena cava interruption when indicated is the best course of action.

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REFERENCE

1. Nelson PH, Moser KM, Stoner C, et al: Risk of complications during intravenous heparin therapy. West J Med 1982 Mar; 136:189-197

Dr. Moser Replies

TO THE EDITOR: Dr. Baird's concerns about thrombocytopenia are certainly warranted. As we indicated, our investigation was not intended to define the incidence of thrombocytopenia or certain other events. Rather, we were interested in what was actually happening in a "slice of practice." One of the things that was *not* happening was daily platelet counts. Whether daily platelet

counts *should* be obtained is, in our judgment, an open issue, as are so many aspects of anticoagulant therapy. Certainly, daily counts would detect thrombocytopenia. The critical issue is whether such a routine would prevent or modify the potential consequences of heparin-induced thrombocytopenia. Arguments could be mounted to support a negative or a positive answer. Future studies dealing with an "outcome analysis" of such a practice are needed and should provide an answer.

Dr. Conti's comments also are welcomed. We found no relationship between bleeding risk and the activated partial thromboplastin time (PTT). As noted in the paper, most studies have found the same lack of relationship. We also agree that judgments as to risk/benefit ratio are the key to proper decision-making in this and other areas of medicine. How one can assure that decisions are made this way is, of course, another matter. We hope that publication of our study is one step in that direction.

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On 'Opening Up' the Health Care System

To the Editor: Dr. Arthur Rivin's article in the March issue[1] is articulate and well-written. However, I patently disagree with his conclusions, and I am surprised that you concurred with him editorially.

The crux of the discussion is under his heading "4. Personal Freedom." Herein he blatantly states that health care is "too complex to expect even the most sophisticated and educated layman . . . to select the proper care . . . without state control of educational requirements." This is the typical elitist rationalization for usurping another's freedom via governmental regulation ("I'm only doing this for your own good . . ."). I do not need to enumerate further examples to this sophisticated readership of the many ways the statists and collectivists in our country have steadily eroded the rights of the individual.

Licensure simply creates a monopoly that is maintained by governmental force and involves them in every aspect of medical care. This does not work to the advantage of either the patients or the physicans. The patients desire competent, compassionate care at a "proper" price. Licensure does little to ensure any of this (witness residency training and board certification).

If delicensure occurred it would not take very long for all sorts of positive educational fallout to occur—for example, more medical programs in the community hospitals informing the public about advances and giving more exposure to the medical staff; community "consumer guides" to physicians listing their credentials, fees and the like and, yes, probably "testimonials," too; a greater number of medical educational programs on community television. And so on.

Let's learn from the mistakes of big business: These dinosaurs are afraid to compete anymore (what free enterprise?) so they form a liaison with government and regulate their competition out of existence, much to the chagrin of the consumer. We don't have to do this. Unlike the days of yore when our capability was mostly psychological support through prestigious mysticism we really can cure or help many of our patients. The radiant, gold-headed Aesculapian cane and top hat have been replaced by the white coat, voluminous medical literature and a burgeoning armamentarium. We do not have to be afraid to compete in the free market.

For a succinct but very complete discussion of this topic I urge interested readers to write Charles W. Johnson, MD, 7702 Louis Pasteur Drive, San Antonio, TX 78229, and ask him for his essay on medical licensure.

GREGORY POLITO, MD
Whittier, California

REFERENCE

1. Rivin AU: 'Opening up' the health care system—Public protection and personal freedom (Commentary). West J Med 1982 Mar; 136:261-264

Refer to: Watts MSM, Bayley C, Healy FA, et al: Ethical problems in medical practice—A protocol for the guidance of physicians (Medical Ethics). West J Med 1982 Jul; 137: 83-86

Ethical Problems in Medical Practice

A Protocol for the Guidance of Physicians

MALCOLM S. M. WATTS, MD, *San Francisco;* SISTER CORRINE BAYLEY, CSJ, *Orange, California;* FRANCIS A. HEALY, MD, *Burlingame, California;* WILLARD S. OSIBIN, MD, *Templeton, California;* MINDY WERNER, BA, *and* LAURENS P. WHITE, MD, *San Francisco*

PHYSICIANS ARE increasingly confronted with "ethical" problems in their professional practice. In each instance the responsible physician is expected and desires to do or to advise that which is ethical or right. Sometimes the right thing to do or recommend is obvious and the decision is easy. But sometimes it is not. The purpose of this report is to offer physicians a framework or protocol for analyzing any ethical problem they may encounter in their medical practice and to provide some guidance toward what might be "ethical" behavior in any particular "ethical" situation.

In any consideration of ethical problems in medical practice it is easy to become mired in the many diverse, often overlapping and poorly understood meanings of words such as *ethics, moral, morality* or even *etiquette*. Except for the generic term *ethical problems in medical practice,* these words are not used in this discussion.

This report makes no attempt to displace or change the very broad "Principles of Medical Ethics of the American Medical Association" or the often quite specific "Current Opinions of the Judicial Council of the American Medical Association." Rather it seeks to augment those documents by providing a kind of protocol or algorithm to assist physicians to find their way through the complexities of difficult ethical problems they may encounter in their practice.

A Report of the Committee on Evolving Trends in Society Affecting Life, California Medical Association. The authors made up the Subcommittee on Ethics. The report was prepared in 1981.

Reprint requests to: Michael W. Jones, Staff Coordinator, CMA Committee on Evolving Trends in Society Affecting Life, 731 Market Street, San Francisco, CA 94103.

General Assumption

The following assumptions are basic and are considered to be given:

- The primary concern of the physicians must always be with what is best for the patient.
- The physician has the responsibility and the duty to apply his or her professional knowledge, skills, sensitivity and clinical judgment to advise or make recommendations concerning medical interventions.
- The patient has the right to make the final decision with respect to his or her own care, unless not competent to do so—in which case this is the responsibility of the legally authorized representative of the patient.

Outline of Steps in the Protocol

Ethical problems in medical practice are found to arise when there are conflicts between or among the interests (1) of the patient, (2) of the physician or (3) of one or more third parties. The following is an outline of the steps to be taken in the protocol that will be described:

1. State the *ethical problem.*
2. Identify the *conflict* or *conflicts* that pertain to the ethical problem.
3. Define each of the *interests* at stake in the conflict or conflicts which were identified.
4. Determine the *authority* of each of the parties at interest in the conflict or conflicts.
5. Examine any *"contracts"* (to be defined below) that may pertain to the ethical problem.
6. Apply the *"rules"* (to be defined below) as they may be appropriate to the problem as

analyzed in terms of the construct of conflicts, interests, authorities and contracts.

Each of the above items will apply to a greater or lesser extent to any ethical problem in medical practice. As each is tested against a specific problem, those with the greatest applicability to the problem will emerge and provide some guidance for a physician confronted with an ethical problem in his or her practice.

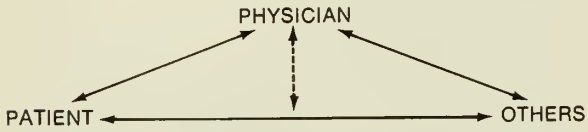
Definitions

Ethical Problem

An ethical problem in medical practice exists when there is a genuine conflict of interests in patient care.

Conflict

The arrows in the diagram below indicate where conflicts can occur between major parties at interest in patient care:



It should be noted that a physician may also be a party to conflicts between patient and others as indicated by the dotted line (for example, when a patient's interests conflict with available resources which in turn conflict with the physician's primary responsibility to a patient and another responsibility to society, and perhaps to other patients, for prudent use of scarce resources for patient care).

Interests

The interests of each of the parties in conflict with respect to the stated ethical problems must be defined. These include the personal interest of the physician, the individual interest of the patient and the interest of any third parties or others who may be involved (see Figure 1).

Physicians are seen to have self-interests, family interests and professional interests. Self-interests may include health, well-being and a desire for reasonable remuneration. Family interests may include health, well-being and duty to family. Professional interests include personal attitudes, professional competence to determine what is wrong, what is likely to happen and what can be done about it, and professional fulfillment and satisfaction.

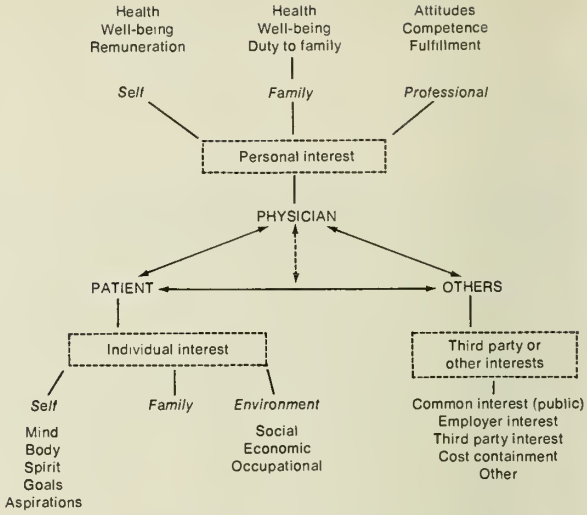


Figure 1.—Interests That May Be in Conflict.

The individual interests of patients relate to self, and family and other environmental factors affecting the patient. Self includes health and well-being of mind, body and spirit, as well as personal attitudes, goals and aspirations. Interactions with family may have an important bearing on the patient interest, as can social, economic, occupational or other environmental factors. Each of these should be identified and defined to the extent practicable.

The interests of others include the common or public interest, third party interests, employer interests as these may affect either physician or patient, cost containment, prudent use of limited resources and the like.

Authorities

Authority is seen to lie with all three—physician, patient and others, including the public. The physician's authority derives from professional knowledge, sensitivity, skills and license to practice. The patient's authority lies in a right to control what is done with his or her own body and in the legal doctrine of informed consent. Others, the public and society express their authority in the law or in what will or will not be paid by third parties in patient care, for example. Each has a responsibility to exercise his, her or its authority.

"Contracts"

"Contracts" are more in the sense of "social contracts" than written agreements. There is an implicit understanding in the doctor-patient relationship in which the doctor agrees to provide

care in cooperation with the patient. There is an implicit understanding between physicians and society in which physicians are given license to do things forbidden to others in return for a commitment to use their knowledge and skills and license privileges for the benefit of patients and the public. An example of a "contract" between patient and society might be right of access to care or the guaranteed funding of the costs of end-stage renal disease under the Medicare law. "Contracts" such as these appear to pertain to situations in which ethical problems in patient care arise.

"Rules"

Five different "rules" are identified that the physician can apply with varying emphasis depending upon the ethical problem and the particular situation:

1. *Societal Rule.* This refers to what is done, what is custom, what is widely accepted, what is law.

2. *Rule of Mutual Trust.* This refers to the element of trust inherent in each of the contracts defined above. For example, the trust rule would require that a physician honor the trust in a physician-patient relationship by disclosing any conflicts of interest the physician might have in that situation.

3. *Golden Rule.* The Golden Rule, to do as one would wish to be done by others in the given situation, brings all of a physician's knowledge, sensitivity and skills directly to bear in deciding what to do or recommend in a difficult situation.

4. *Religious Rule.* For some physicians, patients and even some others (in the sense of some hospitals or health care institutions), religious beliefs or principles may govern behavior when these bear upon ethical problems in medical practice.

5. *Professional Rule.* The professional rule, sometimes called the "company rule," is where professional etiquette, the "American Medical Association's Principles of Medical Ethics" and the "Current Opinions of the Judicial Council of the American Medical Association" can be brought into play in dealing with ethical problems in medical practice.

Applying the Protocol—A Case Study

Ethical Problem

A child is born with Down's syndrome and a duodenal atresia. The parents refuse consent for corrective surgical procedures on the atresia because they do not want to raise a child with the abnormalities of Down's syndrome. Should the physician go along with the parents, reasoning that they have a responsibility and therefore a right to make a decision of this kind? Or should the physician intervene and attempt to get authorization for the operation?

Identification of Conflicts

- Physician⟷Patient (Child)
- Patient (Child)⟷Others (Parents)
- Physician⟷Others (Society, Parents)

Definition of Interests Involved in Each Conflict

- Physician⟷Patient (Child)

A physician's interest is to bring professional knowledge, skills and sensitivity to bear in best interest of patient. Patient (child) is unable to express his or her own interest. What is the best interest of the patient?

- Patient (Child)⟷Others (Parents)

The patient is unable to express own interest. Parents are legal guardians of the patient's interest. Is the parents' interest the same as the patient's interest?

- Physician⟷Others (Society, Parents)

The physician's interest is in what is best for the patient (child). Society and parents have social and economic interests that may or may not be in the best interest of the patient. The physician also has responsibilities to parents and to society.

Authorities

The authority of the physician lies in the power to intervene or not to intervene with the courts in what he or she perceives to be in the best interest of the child who is the patient.

The authority of the patient to control what is done or not done with his or her own body lies not with the patient but with the parents.

The authority of others, that is society, lies in the courts, which might or might not, in behalf of the patient, order the operation to be done over the opposition of the parents.

"Contracts"

The doctor-patient relationship "contract" in this case is with the child rather than the parents.

The implicit "contract" between physicians

and society calls upon physicians to serve both patients and society and these cancel out in this case.

Society holds that persons have a right of access to medical care and this seems to be applicable in this case.

Applying the Rules

1. *Societal Rule.* There is no clear societal rule that seems to apply specifically to this case.

2. *Rule of Mutual Trust.* This rule requires the physician to act in what professional knowledge, skills and sensitivity lead him or her to believe is the best interest of the patient. This rule applies.

3. *Golden Rule.* This rule introduces the physician's personal philosophy and beliefs. It does not seem appropriate to apply this rule in this case.

4. *Religious Rule.* For most physicians there is no religious rule to govern behavior in this case.

5. *Professional Rule.* There is no professional or "company" rule that applies in this case.

Conclusion

The rule of mutual trust emerges as dominant. The patient is unable to speak for himself or herself. It appears that the parents may or may not be acting in the best interest of the child. The committee concluded that the physician should exercise the power to intervene with the courts on behalf of the patient, whose wishes could not be known, and seek a court order to carry out the needed operation.

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DESCRIPTION: Each gram contains: Aerosporin® (Polymyxin B Sulfate) 5,000 units, bacitracin zinc 400 units, neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs; in tubes of 1 oz and ½ oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically* (as an adjunct to systemic therapy when indicated), for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection. *Prophylactically*, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML

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(Continued from Page 19)

Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 2—**TMJ: What Is It and What To Do About It.** Scripps Clinic and Research Fndn. at Hilton, San Diego. Saturday. 6 hrs. $90. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 2-3—**The Skin from A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Saturday-Sunday.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Sci. Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 4-7—**Practical Electrocardiography—ECG Course for Primary Physicians.** Memorial Hospital Medical Center of Long Beach at Caesar's Palace, Las Vegas. Monday-Thursday. 14 hrs. $225. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 4-9—**Review Course in Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center of Long Beach at Sheraton Newport, Newport Beach. Monday-Saturday. 48 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 7-9—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. $275.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 9—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hosp. Medical Ctr.-UCI Ctr. for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 9-10—**Update on Bone and Calcium.** UCSF. Saturday-Sunday.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Soc. at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 29 hrs.

October 9-17—**7th Annual International Body Imaging Conference.** West Park Hospital at Sheraton Royal Waikoloa Hotel, Kona, Hawaii. One week. 28 hrs. $385. Contact: Conf. Sec., Dept. of Radiology, West Park Hosp., 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 280.

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. 30 hrs. Contact: Geri Goodenough, Office of Sci. Mtgs., APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 10-15—**Annual Meeting of American Society of Plastic and Reconstructive Surgeons, Plastic Surgery Educational Foundation, and American Society of Maxillofacial Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. Contact: Linda Campbell, Mtg. Dept., ASPRS, 233 N. Michigan Ave., Suite 1900, Chicago 60601. (312) 856-1818.

October 10-15—**Reproductive Health Care: Changing Concepts in Fertility Regulation.** Wayne State Univ. at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ. Sch. of Med., Med. Research Bldg., Rm. 416, 5500 E. Canfield, Detroit 48201. (313) 577-1011.

October 11-13—**6th Annual Cancer Symposium.** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, Mtg. Coordinator, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 11-15—**Emergency Medicine.** USC. Monday-Friday.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

October 11-15—**12th Annual Review Course in Gynecology and Obstetrics.** USC at Hilton, Pasadena. Monday-Friday. 35 hrs. $450.

October 13—**Post-Operative Complications—Their Prevention and Management.** LLU. Wednesday. 4 hrs.

October 13—**12th Annual Respiratory Medicine Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

October 14-16—**Western Society of Allergy and Immunology—21st Annual Scientific Session.** Hyatt at Union Square, San Francisco. Thursday-Saturday. Contact: Joyce M. Gullixson, Exec. Sec., 1700 S.W. Columbia, Portland 97201. (503) 224-6159.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 15-17—**Neurolinguistic Programming: Sex and Couples Therapy.** Institute of Sexual Behavior and Institute for Medical Education and Research at Village Inn, La Jolla. Friday-Sunday. 18 hrs. $200. Contact: Inst. of Sexual Behavior, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 15-17—**Substance Abuse Prevention Through Effective Parenting.** Isla Vista Health Projects, Inc., and San Diego State Univ. Student Health Services at Village Inn, La Jolla. Friday-Sunday. $150. Contact: Parenting, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 16—**Review Course for Gynecologic Pathology.** USC at Hilton, Pasadena. Saturday. 6 hrs. $75.

October 16-17—**Medical Psychiatry.** UCSF. Saturday-Sunday. 12½ hrs. $115 before October 1; $135, thereafter. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus, Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

October 20—**New Concepts in Diabetes.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 21-24—**International Symposium on the Mitral Valve.** Scripps Clinic and Research Fndn. at Hotel del Coronado, Coronado. Thursday-Sunday. 23 hrs. $350. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

(Continued on Page 41)

J.J.SMITH,M.D.
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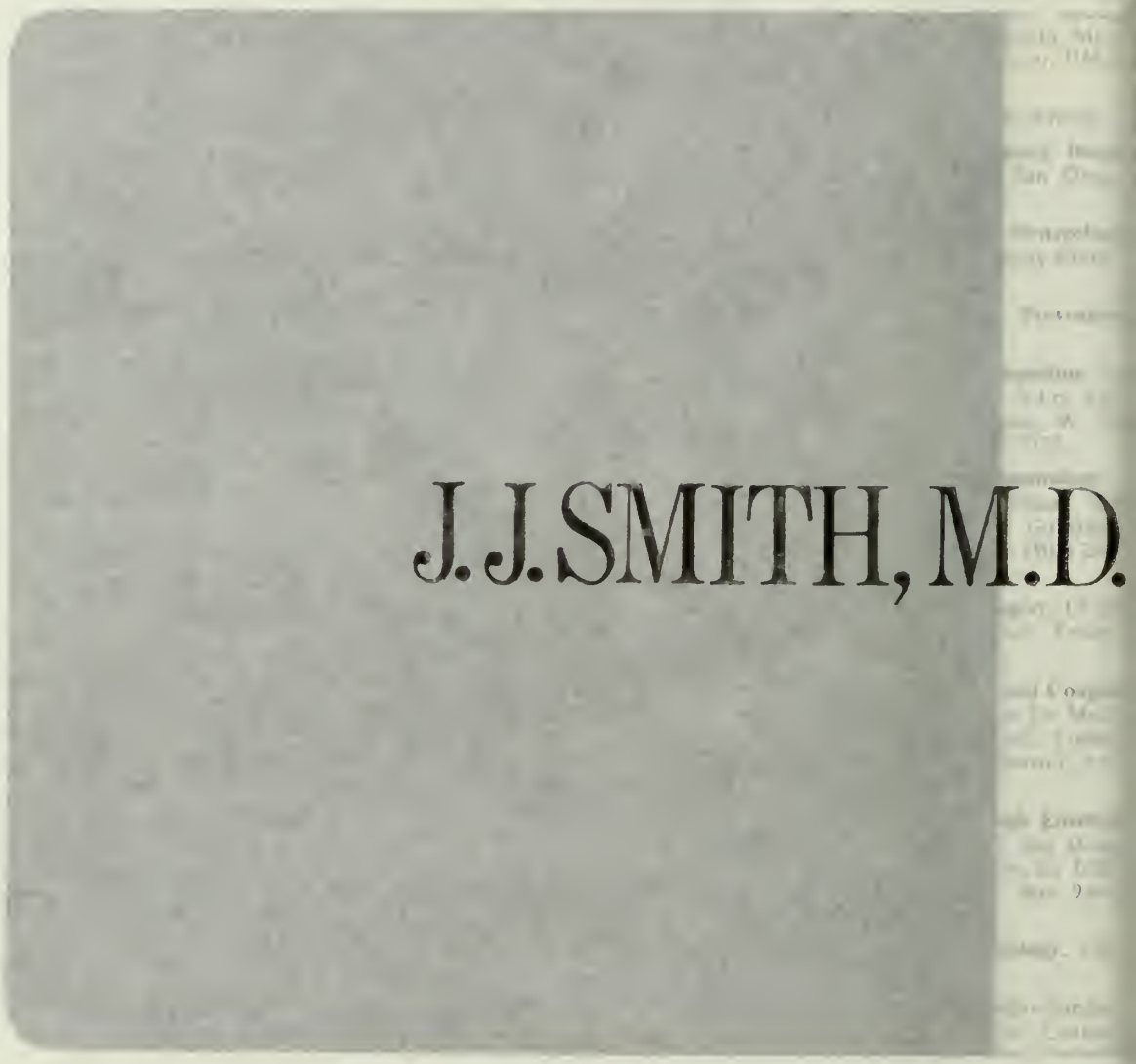
YOUR EXPERT HELP

COUNSELING MAY HELP HER CONCERN



*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomfo Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CA

UT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms

Please see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and on other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma - palliative therapy of advanced disease
9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)
"Probably" effective: For estrogen deficiency induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2.1 to 3.1 fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome, tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice, chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum; hemorrhagic eruption, loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism: 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure: 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression): 1.25 mg daily, cyclically.
3. *Given for a few days.* Prevention of postpartum breast engorgement: 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer: 1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women: 10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865: Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866: Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867: Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868: Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream: No. 872. Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available: Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube.

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(Continued from Page 36)

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 22-24—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $275. Contact: Howard D. Groveman, MD, UCSD School of Medicine (M-022), La Jolla 92093. (714) 452-4613.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

October 23-25—**OB and GYN Endocrinology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Monday.

October 23-30—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela. One week. 20 hrs. $275. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

October 28-30—**Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 28-30—**2nd Bi-Annual Course in Lower Extremity Trauma: Treatment, Complications and Controversies.** Bone and Joint Disease Foundation at Vacation Village, San Diego. Thursday-Saturday. Contact: Lower Extremity Trauma, P.O. Box 9494, San Diego 92109. (714) 282-9316.

October 29-31—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sahara, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 30-November 5—**American Academy of Ophthalmology.** Moscone Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

October 31-November 3—**The Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo. Sunday-Wednesday. 19 hrs. Contact: Dianne Tisue, Dept. of Academic Affairs, 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

November 1-3—**Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo Inn, San Diego. Monday-Wednesday. 19 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037.

November 1-4—**Interstate Postgraduate Medical Association—Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., IPMA, P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

November 4-6—**Sterling Bunnell Memorial Lectureship.** UCSF (Dept. of Orth. Surg.). Thursday-Saturday.

November 5-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 7-12—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui. Sunday-Friday. $350.

November 7-13—**Allergy and Immune Diseases.** Symposium Maui, Inc., and Hawaii Chap., AAFP, at Lahaina Resort, Kaanapali, Maui. One week. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, HI 96761.

November 10—**Pediatric Emergencies.** LLU. Wednesday. 4 hrs.

November 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

November 11-13—**First National Conference on Infantile Apnea and Home Monitoring of High Risk Infants.** Eisenhower Medical Center and Medical Center of Tarzana. Thursday-Saturday. Contact: Annenberg Center for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 340-3911, ext. 1661.

November 11-14—**Controversial Areas in Surgery of the Head and Neck.** Institute for Medical Education and Research at Hilton Beach and Tennis Resort, San Diego. 20 hrs. $250. Contact: IMER, P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS Omaha NE 68101. (402) 551-0801.

November 12-14—**28th Annual Group Therapy Symposium.** UCSF at Holiday Inn, Berkeley. Friday-Sunday. 18 hrs. $125. Contact: Aveleen Blumenstock, Asst. Dir., Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

November 14—**The Lung in 1982.** Granada Hills Community Hospital and UCLA at Sheraton-Universal, North Hollywood. Sunday. Contact: Germaine Trasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

November 14-17—**California Academy of Family Physicians—Annual Meeting.** Hotel del Coronado Coronado. Sunday-Wednesday. Contact: CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 19-22—**Pediatric Update.** Calif. Chapters, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 3-4—**The Anterior Cruciate Ligament "State of the Art."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 3-5—**Clinical Management of Coronary Disease and Dual-Mode Exercise Testing.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8651.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Fndn. at Hilton Beach

(Continued on Page 48)

CALIFORNIA MEDICAL ASSOCIATION

Regional Postgraduate Institutes

GERIATRICS

Hotel del Coronado, San Diego
September 30-October 2, 1982

WEST COAST COUNTIES

Doubletree Inn, Monterey
October 28-30, 1982

PROGRAM PLANNERS:

Doctor John C. Beck, Director
University of California's Multicampus
Division of Geriatric Medicine

Doctor Robert Kane
University of California, Los Angeles
Division of Geriatric Medicine

PROGRAM OBJECTIVES:

- to provide information to combat myths concerning the elderly and health care needs
- to update the participants on diagnosis and treatment of illnesses which occur more frequently in the elderly
- to sensitize the participants to the special physiological and psychological needs of the elderly

TOPICS:

CARDIOLOGY INCLUDING WORKSHOP on Beta Blockers and Calcium Channel Blockers

DIABETES INCLUDING WORKSHOP on Treatment Strategies for Insulin Dependent Patient

FIBROMYALGIA

RESISTANT ORGANISMS

LIFE STYLE, FOODS AND DRUGS

ACUTE DISSEMINATED ENCEPHALOMYELITIS

These programs are accredited for Category One credit.
Hotel space is limited—early reservations are suggested.
Complete program and hotel information will be sent by return mail.
Use the tear-off sheet below or call CMA (415) 777-2000, extension 143.

CMA REGIONAL POSTGRADUATE INSTITUTES

I plan to attend the following Postgraduate Institute(s):

☐ **GERIATRICS**
September 30-October 2, 1982
Hotel del Coronado, San Diego

☐ **WEST COAST COUNTIES**
October 28-30, 1982
Doubletree Inn, Monterey

FEE: $75.00 for **each** institute
($125.00 for non-CMA members)

Please make check payable to
California Medical Association

Name_____ Specialty_____

Address_____

City_____ Zip_____

Number of years out of Medical School_____

Mail to: California Medical Association, 731 Market Street, San Francisco, CA 94103
Attention: Janice Rigney. A program and hotel reservation form will be sent to you.

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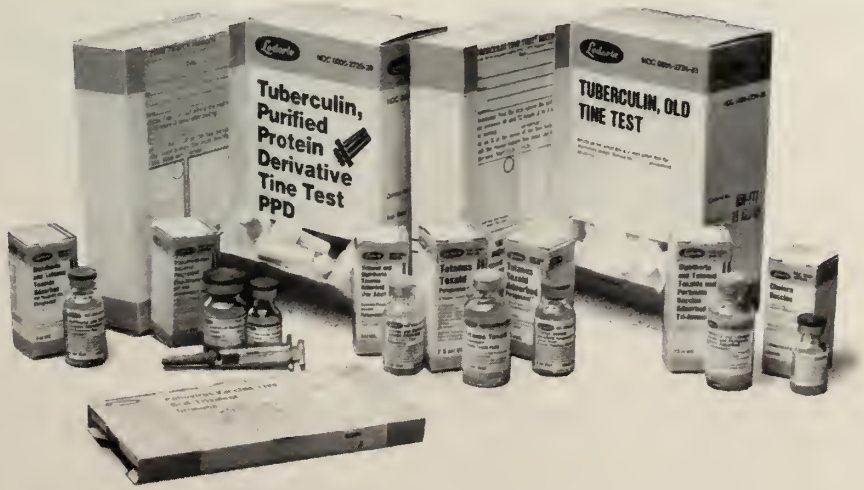

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(Continued from Page 22)

PHYSICIANS WANTED

FAMILY PRACTICE—We are two PAs, one Internist looking for one FP. Rural South Central Washington. But close to everything out-of-doors. Salary to start, then partnership. Ronald C. Myron, Grandview Family Practice Clinic, 242 Division, Grandview, WA 98930.

IDAHO NEEDS NEUROSURGEON. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity, affiliate with 162 bed hospital with rehab. Contact M. Kutsurelis, Assoc. Adm., Mercy Medical Center, 1512 12th Avenue Road, Nampa, ID 83651. Phone (208) 467-1171.

CARDIOLOGIST—Certified, experienced in invasive and non-invasive techniques for association with established cardiology office. Write or call: E. C. Gaulden, MD, FACC, 17541 Irvine Blvd. #B, Tustin, CA 92680; (714) 939-2655.

ORTHOPEDIST or Medical or Surgical Subspecialist needed for fully equipped small primary care medical group (2 FPs, 2 Gen. Int., 1 Gen. & Vasc. Surg.) in beach orientated Northern California city to complement and complete this busy group. Excellent startup arrangements. 2 good hospitals. Write: H. L. LaFont, MD, Capitola Medical Group, 528 Capitola Ave., Capitola, CA 95010.

GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guarantee with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 East 4th North, Logan, UT 84321.

GENERAL/FAMILY PRACTICE PHYSICIAN needed by 35 member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Reply: Mr. D. R. Molesworth, Administrator, San Luis Medical Clinic, Ltd., 1235 Osos Street, San Luis Obispo, CA 93401.

Assistant Professor of Orthopaedic Surgery

University of California, San Francisco, has an opening for an orthopaedic surgeon who is board certified or board eligible within one year. A balance of interest in teaching, patient care and research is necessary. Duties include undergraduate and postgraduate teaching, clinic and inpatient service supervision, clinical and/or laboratory investigative work. Salary negotiable. Liberal fringe benefit program.

Inquiries and curriculum vitae should be directed to: James M. Morris, MD, Chairman, Search Committee, Department of Orthopaedic Surgery, U471, University of California, San Francisco, San Francisco, CA 94143. Telephone: (415) 666-2280, 666-2495.

UCSF IS AN EQUAL OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER

PHYSICIANS WANTED

ASSISTANT CHIEF OF MEDICINE, EMANUEL HOSPITAL, PORTLAND, OREGON. A vacancy exists in this fully accredited Internal Medicine Training Program for an Assistant Chief of Medicine. Send CV to T. M. Andrews, PhD, FRCP, Chief of Medicine, Emanuel Hospital, 2801 N. Gantenbein, Portland, OR 97227.

PHYSICIANS WANTED

PHOENIX: Full-time forensic psych. Maricopa County jail system. Board-elig/cert. Salary $65,000+/year. Contact: Dr. M. Berger, Psych Dir. Correctional Health Services, 3225 W. Durango Phoenix, AZ 85009. (602) 256-1985.

(Continued on Page 46)

Army Medical Department Opportunities

The Army Medical Corps offers virtually unlimited opportunities to learn, teach, investigate, practice and direct. For physicians who want more in their health care career than a predictable daily routine, the Army Medical Corps has a lot to offer. There are challenging professional opportunities in patient care, preventive medicine, research, administration and education. A variety of excellent educational programs exist. As a member of the Army Medical Corps, you become a part of one of the largest comprehensive systems of health care in the United States. Numerous medical facilities exist in most states, ranging from clinics and hospitals to world-reknowned medical centers. For more information...

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(Continued from Page 44)

PHYSICIANS WANTED

STUDENT HEALTH PHYSICIAN. Join seven other physicians serving 17,000 students, September, 1982. Setting and practice challenging. New clinic just completed. Dedicated compatible staff. Nine month position. Additional summer work optional. Medical teaching appointment possibility. CV to Physician Recruitment Committee, Student Health Service, Washington State University, Pullman, WA 99104, before August 1, 1982. Washington State University is an equal opportunity/affirmative action employer.

PHYSICIAN I—General physician for Student Health Service, California State University, Fresno. 10-month position, appointment effective September 1, 1982. Requires California license, completed internship or equivalent postgraduate year of medical training, ability to work with young adults. University of 15,000 students located in the central valley. Fresno is a pleasant city of 210,000 within easy driving distance of the beautiful Sierra Mountains and the Pacific Ocean. Salary range $3,862 to $4,652 depending on qualifications and experience. Application deadline—July 31, 1982. Applicants please send CV to: Staff Personnel Office, Rm. 164, California State University, Fresno, Fresno, CA 93740. Telephone: (209) 294-2032. An Affirmative Action/Equal Opportunity Employer.

INTERNIST WANTED: Board Certified general internist (or with pulmonary sub-specialty) needed to join busy 4 internist practice in Fremont, California—progressive community with population of 131,000 in Bay Area, 45 minutes from San Francisco. Affiliated hospital is 275 bed medical center. New partner would have no problem building active practice quickly. Send CV to IMA, 39225 State St., Fremont, CA 94538.

FAMILY PHYSICIAN—Board eligible or Board Certified Family Practitioner with experience in normal obstetrics to associate with established three man group with similar training. Modern well equipped office, centrally located and ½ block from modern, well staffed, full service, 200 bed hospital. Practice and recreation opportunities abound. Contact: J. D. MOORE, MD, 2626 Edith Ave. Suite C, Redding, CA 96001. (916) 244-4034.

PART TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part time basis, for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 100 Van Ness Ave., San Francisco, CA. Na patient contact. Future administrative and Congressional decisions could affect the number of physicians and specialties needed.

Selection of consultants will be based on the physician's ability to fulfill the Disability Program's caseload needs. At present it appears the following specialties and subspecialties may be needed:

Orthopedics, Internal Medicine, Pulmonary Medicine, Cardiology, Ophthamology, Otorhinolaryngology, Neurology, Psychiatry.

Selection criteria include:

1. Acceptable training in medical specialty leading to Board eligibility or certification,
2. The level and diversity of training,
3. Current and ongoing clinical practice,
4. The amount and diversity of clinical practice,
5. Availability between 7:00 am and 5:30 pm.
6. Valid license to practice medicine in the United States.

Please indicate your interest in writing not later than July 31, 1982 to:

Contracting Officer
Department of Health and Human Services
50 United Nations Plaza, Room 8
San Francisco, CA 94102

Further information and instructions on submitting your CV will be provided by return mail. We encourage application from women and minorities, and would appreciate it if readers of this notice would bring it to the attention of others who may be qualified.

PHYSICIANS WANTED

TRAUMA SERVICE DIRECTOR—An acute care growth oriented 272+ bed community hospital in Southern California has an opportunity for a board certified general surgeon, preferably with subspecialty training in thoracic or vascular surgery, who has special training and experience in traumatology. Excellent administrative/management capabilities desired. Responsibilities will include patient care, teaching and research. To explore this excellent opportunity please send your curriculum/vitae to: Department TR, Human Resources Department, Box 6307, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ASSOCIATE WANTED

PART-TIME RADIOLOGIST to do general radiology in office. Excellent retirement situation. Beautiful area of Northwest. Box 6298, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PRACTICES AVAILABLE

PRACTICE AND EQUIPMENT. Ophthalmologist retiring, will sell practice and/or equipment for cost of equipment only. Anaheim, California location for the past 20 years. Phone or write for further information to: Joseph S. Holowin, MD, 710 S. Brookhurst Suite A, Anaheim, CA 92804. (714) 772-5740.

TO SELL OR BUY A MEDICAL PRACTICE, or to arrange an association, contact Physicians Clearinghouse, Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762. Consulting, Appraising, Partnerships, Placement.

ENT PRACTICE AVAILABLE in affluent Kansas City, Missouri, suburb for board certified or board qualified candidate. Fully equipped office. Trained office staff. Excellent hospital and professional affiliations. Candidates may call or write, in confidence, to Dr. Ronald L. Hammerle, or Ms. Cheryl Powell, Health Resources. Ltd., River Road Professional Bldg., P.O. Box 14188, Kansas City, MO 64152, or phone (816) 587-0920.

PRACTICES FOR SALE

FAMILY PRACTICE FOR SALE—Solvang, California—Well equipped office, beautiful valley and climate. Call (805) 688-2070.

INTERNAL/FAMILY MEDICINE practice for sale. Solidly established and thriving. In breathtakingly beautiful Northern California seaside resort and retirement community. Includes lovely home and new professional building. Reply Box 4306, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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SITUATIONS WANTED

CALIFORNIA TRAINED INTERNIST—Anxious to return to the Southern West Coast. Currently assistant professor at top midwest university. Box 6297, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PERIPHERAL VASCULAR AND GENERAL SURGEON. ABS, FACS, 6 years intensive surgical practice Northern California wishes to relocate in Southern California in Northern San Diego County or San Diego area. U.S. university trained with fellowship, U.S. born. Also experienced academic medicine, clinical research, teaching, administratively. Reply Box 6301, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL PRACTITIONER, 37, seeks permanent part-year practice opportunity in salt-water community California or Washington. Best references. Write for CV. J. D. Rienstra, MD, 859 6th St., B-201, Bremerton, WA 98310.

LOCUM TENENS SERVICE
WESTERN PHYSICIANS REGISTRY

. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.**

FOR RENT

CENTRAL CALIFORNIA COAST—New offices in group setting. Now you can have the best of both worlds. Practice in a dynamic med/dent group or solo. In two growing areas in one of the best locations in the nation, near Monterey Peninsula. Also much new and used medical equipment for sale. Call now for information on these unusual opportunities. (408) 659-4828.

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LOCUM TENENS WORK WANTED

GENERAL PRACTITIONER, 37, available for locum fall 1982 California or Washington. Please write J. D. Rienstra, MD, 859 6th St., B-201, Bremerton, WA 98310.

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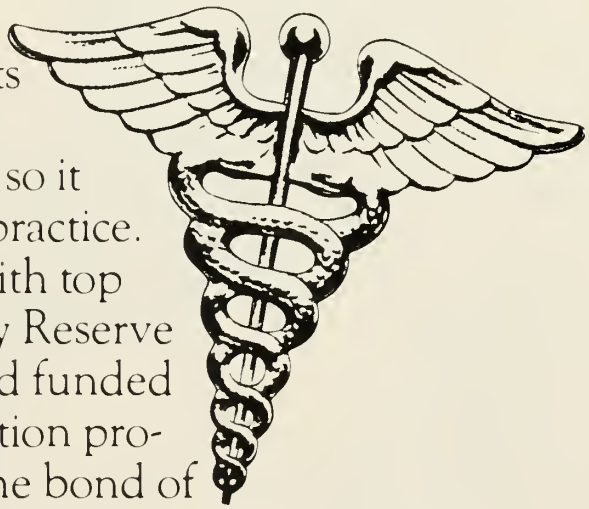

FOR FURTHER INFORMATION CONTACT THE USAR AMEDD PERSONNEL COUNSELOR IN YOUR AREA:

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CPT Lonny Houk, MSC
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CPT James Valentine, MSC
(415) 883-0487

Wyoming, Utah and New Mexico
MAJ Alinga Allen, ANC
(303) 361-3889

Southern California
MAJ James Sheehan, MSC
(714) 836-2866

Idaho, Montana, Oregon and Washington
MAJ Donald T. Cuttie, MSC
(206) 967-2524/5046

ARMY RESERVE. BE ALL YOU CAN BE.

(Continued from Page 41)

Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Ed., Los Angeles 90024. (213) 825-4617.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

December 8—**18th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

December 10-12—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

IDAHO

July 28-31—**Idaho Medical Association 90th Annual Meeting.** Sun Valley. For information contact IMA, P.O. Box 2668, Boise, ID 83761. (208) 344-7888.

See also Utah Listings: August 2-6.

See also Washington Listings: February 14-17.

MONTANA

September 9-11—**Adult and Pediatric Chest Diseases—Current Views 1982.** Bigfork. Thursday-Saturday. Flathead Lake Lodge. Contact: American Lung Association of Montana, 828 Helena Ave, Helena. MT 59601. (406) 442-6556.

September 30-October 2—**Montana Medical Association Annual Meeting.** Great Falls. Thursday-Saturday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category 4 under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 19-22—**25th Annual Ruidoso Family Practice Seminar.** Ruidoso. Monday-Thursday. Inn of the Mountain Gods. 20 credit hours. Also AAFP Prescribed. Contact: Convention Director, NM Academy of Family Physicians, PO Box 456, Sunland Park, NM 88063. (505) 266-7868 or (915) 533-3449.

July 23-25—**11th Annual Santa Fe Cardiology Symposium.** Santa Fe. Friday-Sunday. Inn at Loretto. 14 credit hours, also AAFP Prescribed. Contact: Meeting Director, Southwest Cardiology Associates, 8100 Constitution NE, Albuquerque, NM 87110. (505) 292-1114.

July 29-31—**General Surgical Update—82.** Albuquerque. Thursday-Saturday. Classic Hotel. 15 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

August 27-28—**Pediatric-Adolescent Sports Medicine.** Albuquerque. Friday-Saturday. Hilton Inn. 9 credit hours, also AAFP Prescribed. Contact: Tom Bodnar, Albuquerque & Bernalillo County Medical Association, 303 San Mateo NE, Suite 203, Albuquerque, NM 87108. (505) 268-2446.

September 25—**Margaret E. Prince Lecture on Surgical Aspects of Thyroid and Parathyroid Disease.** Albuquerque. Saturday. Sheraton Old Town. 4 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Elective. Contact: Jonathan Abrams, MD, UNM, School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

October 9—**Medical and Surgical Management of Cerebrovascular Disease Seminar.** Albuquerque. Saturday. Sheraton Old Town. 7.5 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 14-16—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: NM Heart Institute, 2403 San Mateo NE, Albuquerque, NM 87108. (505) 884-3717.

October 15—**Gynecologic Cancer 1982.** Los Alamos. Friday. Los Alamos Medical Center. 6 credit hours. Contact: James M. Cooper, MD, Los Alamos Council on Cancer, Los Alamos, NM 87544. (505) 662-4412.

November 12-13—**New Mexico Medical Society Interim Meeting.** Las Vegas, New Mexico. Friday-Saturday. Highlands University. 7 credit hours, also AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

February 14-17—**Taos Medical Symposium.** Taos. Monday-Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II, MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

(Continued on Page 50)

IOULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

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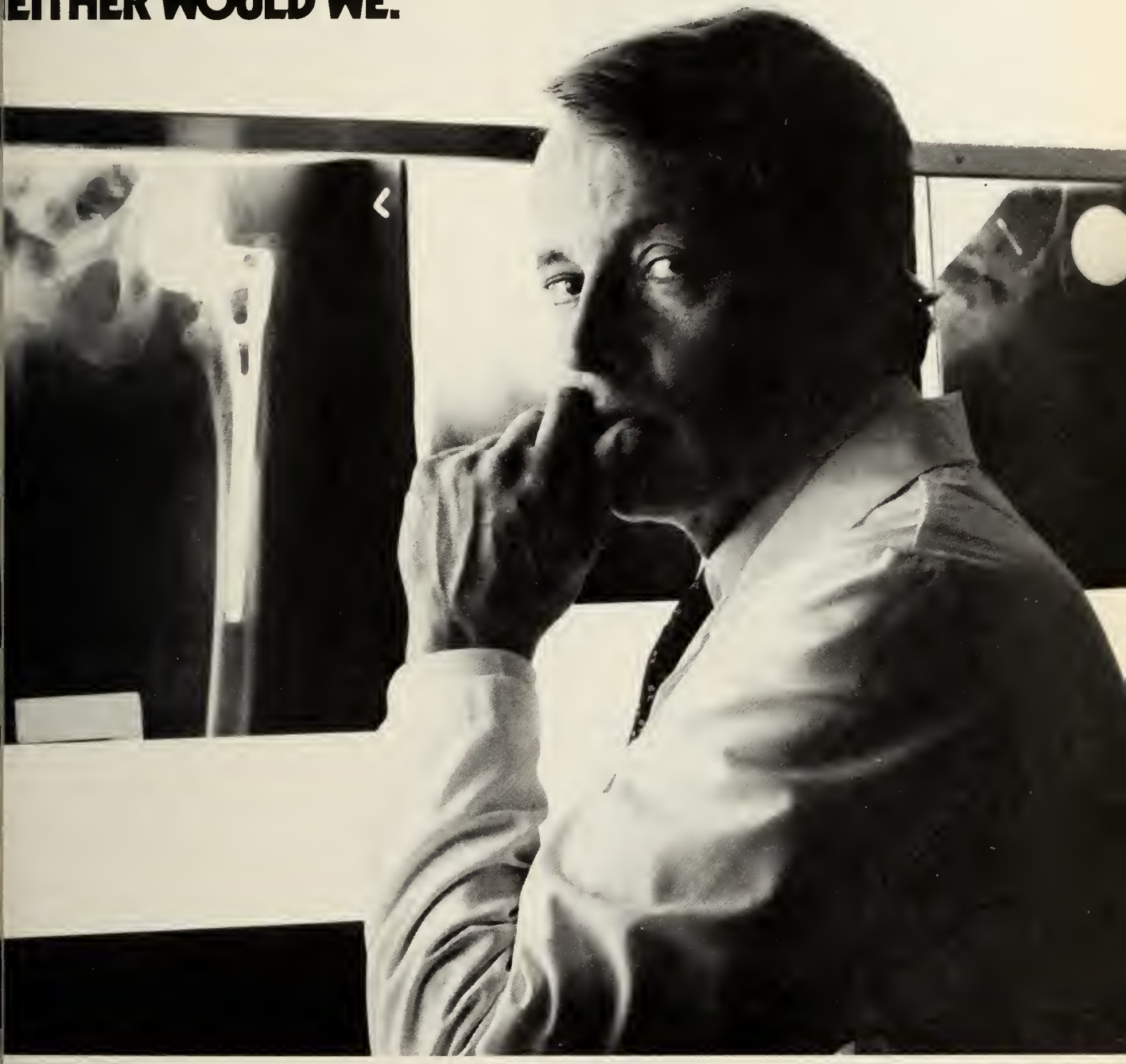

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You must make allowances for potential adversity and you should expect your professional liability insurance company to do the same.

Responsible medical malpractice insurers, like The Doctors' Company, know that their policyholders' long-range interests are best protected by financial strength and solvency.

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AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

(Continued from Page 48)

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD. Douglas Community Hospital, 738 West Harvard Avenue. Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital. 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb. Good Samaritan Hospital and Medical Center. 1015 NW 22nd Avenue. Portland. OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

September 10-11—**Ashland Conference: Antimicrobial Therapy in Perspective: The Place of the New Drugs.** Ashland. Friday-Saturday. Ashland Hills Inn. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

(Continued on Page 53)

RIMSO®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE

RIMSO® - 50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO ® - 50 has not been approved as being safe and effective for any other indication There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None known.

WARNINGS

Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide This hypersensitivity has been reported in one patient receiving intravesical RIMSO® - 50 The physican should be cognizant of this possibility in prescribing RIMSO® - 50 If anaphylactoid symptoms develop, appropriate therapy should be instituted

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations are recommended prior to and periodically during treatment Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count

Intravesical instillation of RIMSO® - 50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation

Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (2 5-12 gm/kg) Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2 5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO® - 50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION

Instillation of 50 ml of RIMSO® - 50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes Application of an analgesic lubricant gel such as lidocaine jelly to the uretha is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO® - 50 can reduce bladder spasm

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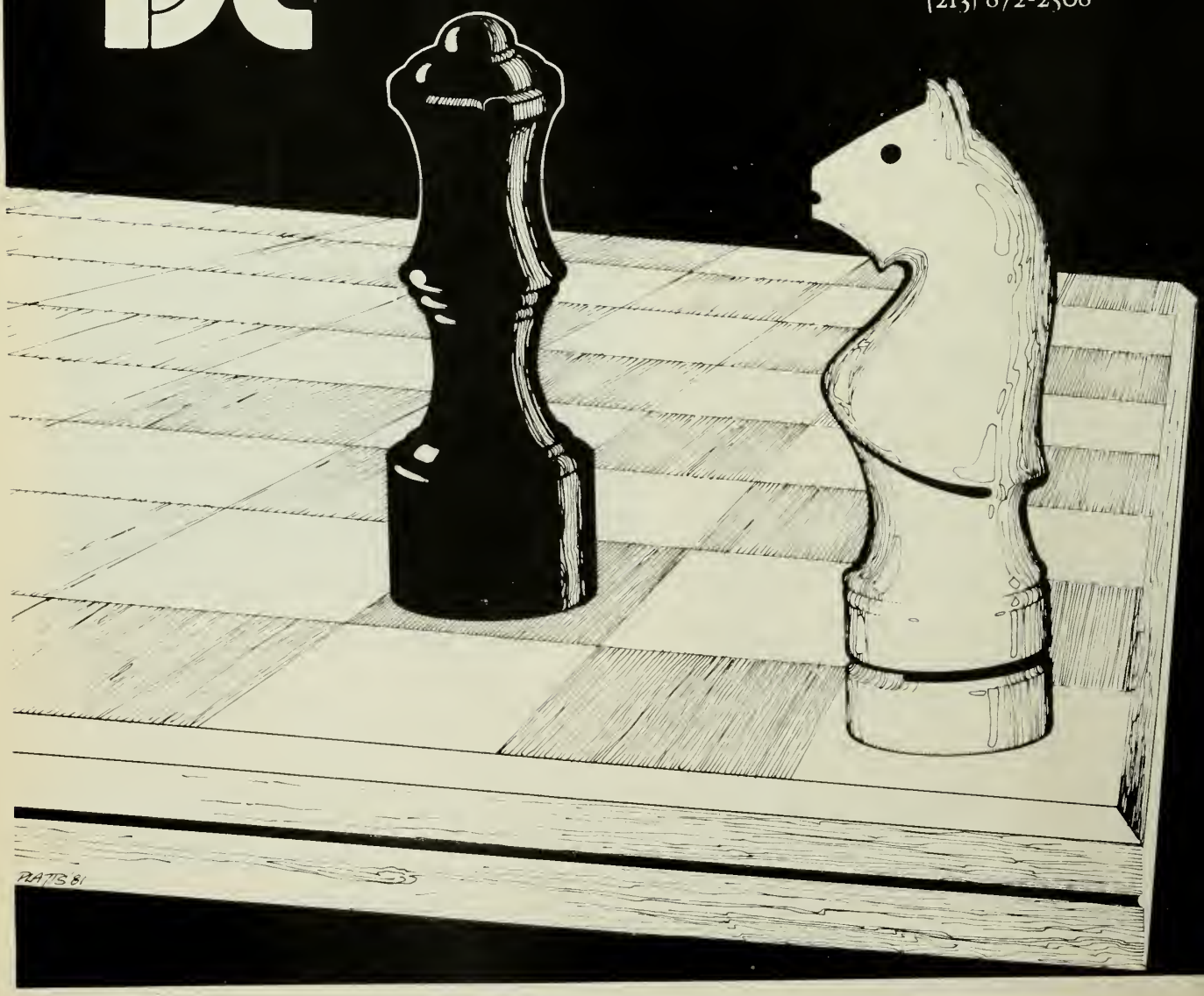

(Continued from Page 50)

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Friday—7:30-8:30 a.m. Contact: Thomas Schwenk, MD, (801) 350-4111.

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Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

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Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

July 21-25—**Current Concepts in Digital Subtraction Angiography, CT of Spine, CT of Temporal Lobe, CT of Pharynx, Larynx, Neck** (Sponsor: University of Utah). Wednesday-Sunday. Jackson Hole, Wyoming. Fee: To be announced. Credit: To be announced. Contact: F. Matsuo, MD (801) 581-8188.

August 2-6—**Pediatric Immunology and Infectious Diseases** (Sponsor: University of Utah). Sun Valley Lodge, Idaho. Fee: To be announced. 25 hrs. Contact: Harry Hill, MD, John Matsen, MD (801) 581-5514.

August 5-6—**Utah Perinatal Association Annual Meeting** (Sponsor: University of Utah). Park City. Monday-Friday. 12 hrs. Fee: $70. Contact: Nan Streeter, RN (801) 277-8458.

September 15-17—**Annual Utah State Medical Association Meeting** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. Fee: To be announced. Credit: To be announced. Contact: Maxcine Fry (801) 355-7477.

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September 17—**Pediatric Ophthalmology Meeting: Eye Problems of Children** (Sponsor: University of Utah). Snowbird. Friday. 6 hrs. Fee: $15-$35. Contact: Jane Kivlin, MD (801) 581-6384.

November 12-13—**New Techniques in Pulmonary Medicine** (Sponsors: LDS Hospital/University of Utah). Salt Lake City. Friday-Saturday. Little America. 10 hrs. $70. Contact: C. Duane Schmidt, MD (801) 353-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

July 15-16—**Surviving the Elements.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

July 23—**Marriage of the Professional.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

July 23-25—**Washington State Society of Anesthesiologists: Seafair IV Anesthesia Meeting.** Seattle. Friday-Sunday. Virginia Mason Medical Center. Contact: VMMC.

July 29-30—**Infertility.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

August 16-20—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress Operations Office, 13th International Cancer Congress, Fourth and Blanchard Building, Suite 1800, Seattle, WA 98121. (206) 621-9440.

September 10—**Leonard Memorial Lecture: Endocrine Day.** Seattle. Friday. Child Developmental and Mental Retardation Center. Contact: U/W.

September 10-11—**Advanced Cardiac Life Support.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

September 10-11—**Short-term Group Psychotherapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

September 16-17—**Plastic Repair and Wound Management.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

September 23-25—**Advances in Internal Medicine.** Seattle. Thursday-Saturday. Contact: U/W.

September 24—**Pathology Day.** Seattle. Friday. Swedish Hospital. Contact: U/W.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

October 8-9—**Annual Cancer Conference: Symptom Management in the Cancer Patient.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 15-16—**The Insulin Pump in Clinical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 22—**Gynecologic Surgery.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 22-23—**Care and Rehabilitation of the Injured Wrist.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 28-29—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 4-5—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

(Continued on Page 56)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. Annual Meeting: 1983—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: 1983—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: July 28-31, 1982, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: September 30-October 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane. Reno 89502. Annual Meeting: 1983—date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. Annual Meeting: 1983—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: June 30-July 3, 1982, Jackson Lake Lodge, Moran.

(Continued from Page 54)

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 12—**Eye Care in General Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 13-14—**Medicine and Religion.** Seattle. Saturday-Sunday. U/W Health Sciences Building. Contact: U/W.

November 19—**Neuroophthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 2-3—**Surgical Aspects of Lung Disease.** Seattle. Thursday-Friday. Contact: U/W.

December 3—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 6-7—**American College of Physicians MKSAP IV.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

December 9-10—**Aging and Elderly.** Seattle. Friday-Saturday. Contact: U/W.

January 21-23—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900. Seattle, WA 98121. (206) 623-4801.

February 14-17—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Thursday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

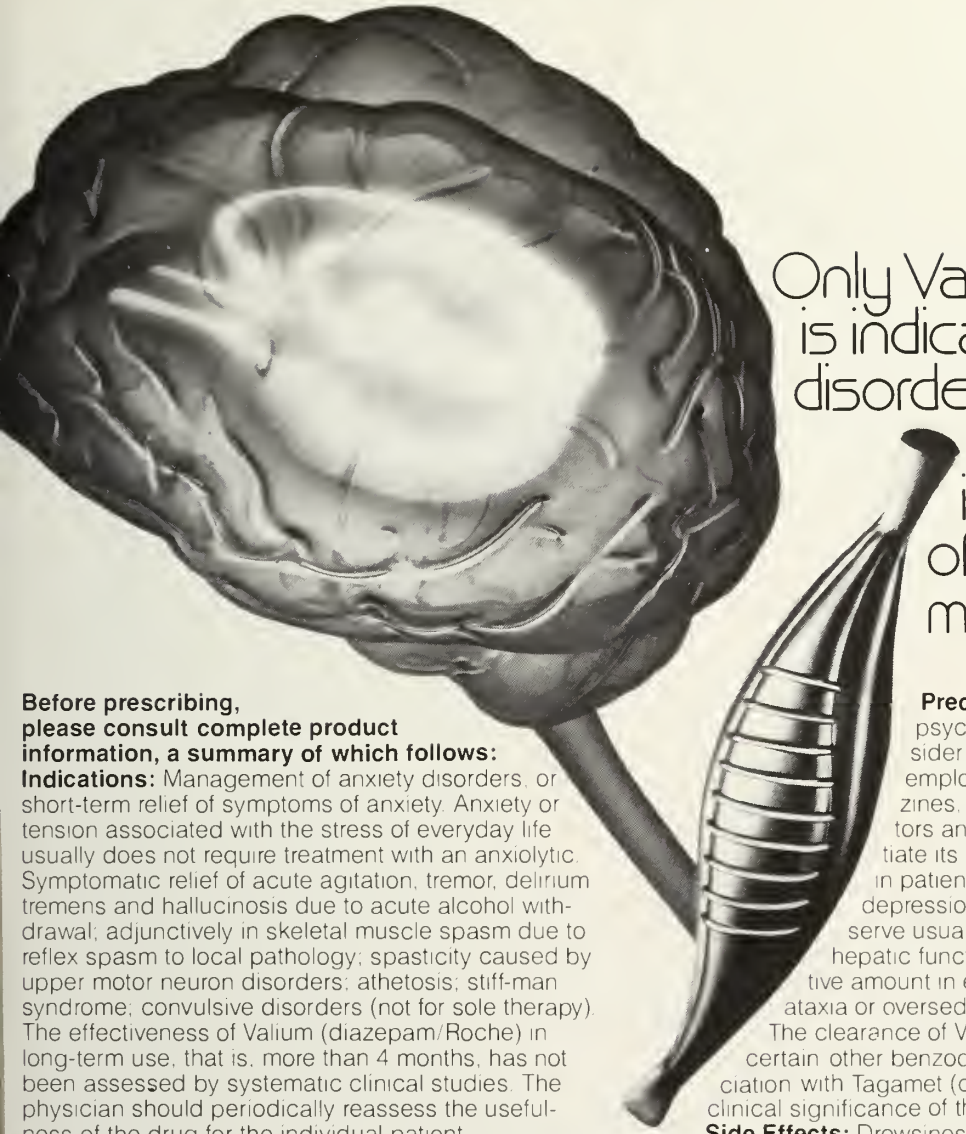
WYOMING

See Utah Listing, July 21-25.

See Washington listing, September 16-18, 1982.

Index to
The Western Journal of Medicine Advertising

AYERST LABORATORIES
Premarin Tabs/Vag Cream 37, 38, 39, 40
BOYLE & COMPANY PHARMACEUTICALS
Triva 5
BURROUGHS WELLCOME CO.
Neosporin 35
CALIFORNIA MEDICAL ASSOCIATION
Regional Postgraduates Institutes 42
CLASSIFIED 22, 44, 46
COOPERATIVE OF AMERICAN PHYSICIANS, THE
Mutual Protection Trust 3
CPS MEDICAL BILLING 30
DelBRON MANAGEMENT SYSTEMS INC 29
DOCTORS' CO., THE 49
ELI LILLY AND COMPANY
Keflex 55
KEY PHARMACEUTICALS
Theo-Dur 20, 21, 22
LEDERLE LABORATORIES
Toxoids 43
NATIONAL MEDICAL ENTERPRISES 53
NORCAL MUTUAL INSURANCE CORPORATION 6
PFIZER
Procardia 24, 25, 26, 27, 28
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 23
PRACTICE SERVICE CORPORATION 52
RESEARCH INDUSTRIES INC.
Rimso-50 51
ROCHE LABORATORIES
Bactrim ..... 2nd cover, 1, 2
Limbitrol 12, 13, 14
Valium ..... 3rd and 4th covers
SALT RIVER PROJECT
Medical Director Recruitment 14
SMITH KLINE & FRENCH LABORATORIES
Dyazide 34
E. R. SQUIBB & SONS, INC.
Corgard 8, 9, 10
STAFF RESOURCES INC 2
3M CLINICAL LABORATORY SERVICES 15
UPJOHN COMPANY, THE
Motrin 33
U.S. ARMY RECRUITMENT 44
U.S. ARMY RESERVE 47
USC SCHOOL OF MEDICINE
12th Annual Review Course—Gynecology and Obstetrics 29
WESTERN JOURNAL OF MEDICINE, THE
Subscription 32
WESTLAND MEDICAL SYSTEMS 45
WYETH LABORATORIES
Ativan Oral 31, 32
Lo/Ovral 17, 18



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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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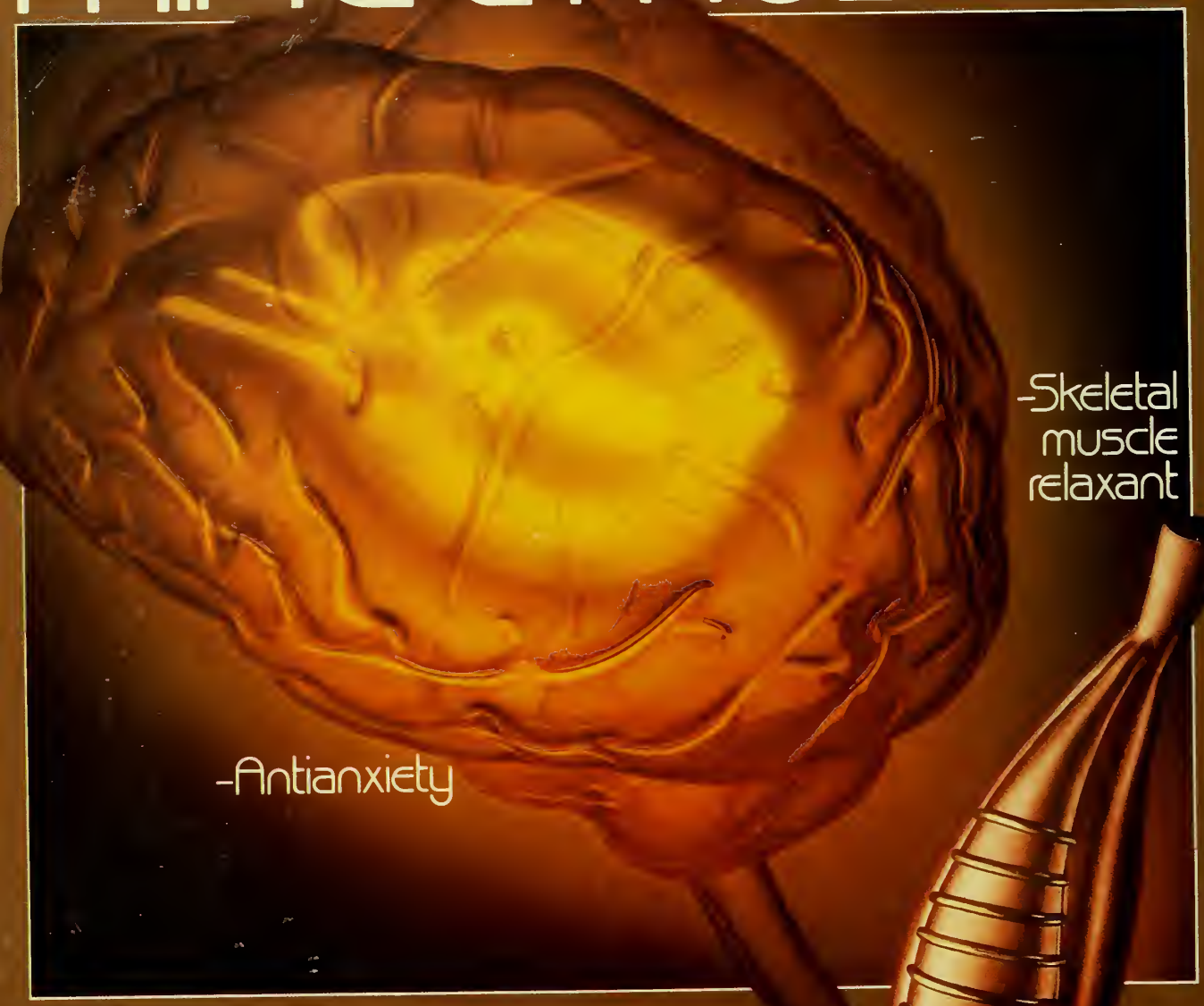

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87 *Acute Cholecystitis: The Diagnostic Role for Current Imaging Tests*
GERBAIL T. KRISHNAMURTHY, MD

95 *Urology/Sexualty Clinic: Results of Counseling of 67 Men*
ALEX L. FINKLE, PhD, MD, and SHIRLEY JACKSON

MEDICAL PROGRESS

99 *The Differential Diagnosis of Pleural Effusions* STEVEN A. SAHN, MD

MEDICAL STAFF CONFERENCE

109 *Rheumatoid Arthritis—From Rubens to Restriction Maps* Chief Discussant: JOHN D. STOBO, MD

IMPORTANT ADVANCES IN CLINICAL MEDICINE

116 *Allergy—Epitomes of Progress*

EDITORIALS

124 • *WJM Welcomes WMS* • *Further Comments on Pleural Effusions* • *Tobacco and Cancer* • *The AMA and a National Health Policy* • *Some Economic and Human Aspects of Cost Control in Patient Care* • *Don't Kid Around* • *On Having Encounters With Patients*

CASE REPORTS

130 *Association of Myoglobinuria With Adenovirus Infection*
HOOSHANG MESHKINPOUR, MD, and N. D. VAZIRI, MD

132 *Polyarthritis Associated With Breast Carcinoma*
MICHAEL KWOK L. CHAN, MD; CHARLES S. HENDRICKSON, MD, and KATHLEEN E. TAYLOR, MD

134 *Metaldehyde Poisoning From Slug Bait Ingestion*
W. T. LONGSTRETH, Jr, MD, and DAVID J. PIERSON, MD

CORRESPONDENCE

138 • *How Much Testing Is Needed?* • *Sickling Crises at High Altitudes* • *Diagnosis of Testicular Torsion* • *Holistic Medicine: Advances and Shortcomings* • *Thrombotic Thrombocytopenic Purpura* • *Needle in the Foot*

TOPICS IN PRIMARY CARE MEDICINE

141 *Infectious Mononucleosis* MAXINE A. PAPADAKIS, MD

SPECIAL ARTICLE

145 *The Costs and Risks of Medical Care—An Annotated Bibliography for Clinicians and Educators*
STEPHEN J. McPHEE, MD; LOIS P. MYERS, MPP, and STEVEN A. SCHROEDER, MD

PREVENTIVE MEDICINE

162 *Infant Passenger Safety Education in Perinatal Services in California*
ALBERT CHANG, MD, MPH, and ESTHER LEVY, MS

INFORMATION

166 *'Loads' Alert* ALI M. KHAJAWALL, MD; JOHN J. SRAMEK, Jr, PharmD, and GEORGE M. SIMPSON, MD

169 *The Bedside Sherlock Holmes* FAITH T. FITZGERALD, MD, and LAWRENCE M. TIERNEY, Jr, MD

176 *In Memoriam*

180 *Book Reviews* • *Books Received, See Advertising Page 46*

Detailed Table of Contents, See Advertising Pages 7 and 11

Information for Authors, See Advertising Page 54

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 15)**

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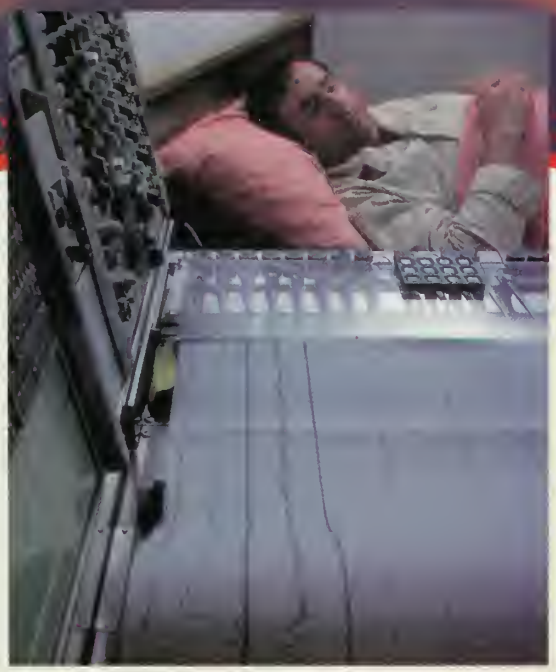

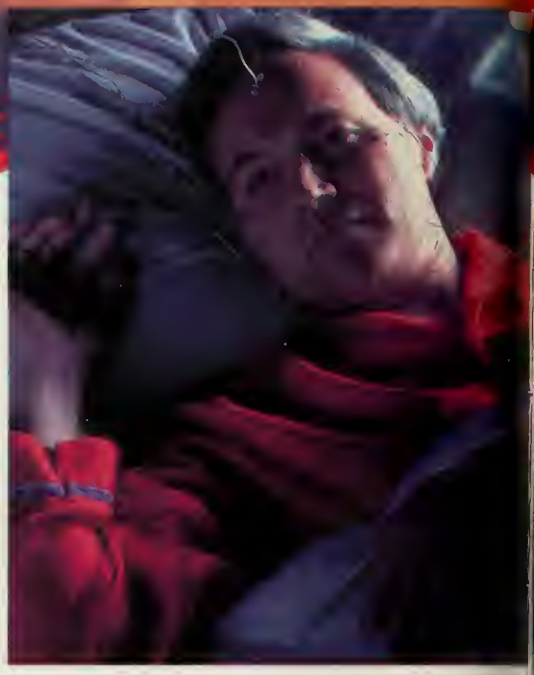

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Difficulty falling asleep is often the primary complaint of insomnia patients.[1,2] And when a hypnotic fails to reduce sleep induction time at the prescribed dosage level, some patients may be more susceptible to multiple dosing on their own.[3] So prompt sleep onset can be an essential consideration in the choice of hypnotic therapy.

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2. Less time awake after sleep onset

In sleep laboratory studies, Dalmane reduced wake time after sleep onset by 61% ($p < 0.05$) on the first three nights of therapy. Temazepam and pentobarbital failed to maintain efficacy in this parameter through two weeks of therapy; however, Dalmane continued to be effective through 28 consecutive nights.[6]

3. Less total time awake

Helping patients sleep longer and with fewer awakenings is another therapeutic goal where Dalmane stands apart. Dalmane decreased total wake time by 51% ($p < 0.01$) on the first three nights of therapy in sleep laboratory studies—a level of significant improvement unsurpassed by any other hypnotic tested.[4]

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And when compared with placebo baselines in the sleep laboratory, Dalmane (flurazepam HCl/Roche) produced a 35% ($p < 0.01$) decline in nocturnal awakenings.[7] Together these results point to the efficacy of Dalmane in helping the insomniac patient achieve a more restful night's sleep.

4. Low incidence of morning hangover

Sleep laboratory findings on the quality of Dalmane-induced sleep are complemented by clinical studies on the quality of awakening after a night on Dalmane. In one study comparing Dalmane with placebo, the vast majority of patients ($p < 0.001$) reported they "slept better" and awoke feeling refreshed and alert after taking Dalmane.[8]

Another retrospective study of 2542 hospitalized medical patients showed only a 3.1% incidence of residual drowsiness—"morning hangover"—with Dalmane.[9] While residual effects are usually dose-related, patients should be cautioned about drinking alcohol, driving or operating hazardous machinery during therapy. Since the risk of oversedation, dizziness and/or ataxia increases with larger doses in the elderly, the 15-mg dosage is generally recommended. It is contraindicated in pregnancy.

5. Avoids rebound insomnia

Rebound insomnia—a statistically significant worsening of insomnia after hypnotic therapy is discontinued—is a potential clinical hazard with some hypnotics.[10,11] In 1 of 2 sleep laboratory studies, a comparison of pre- and posttherapy sleep parameters showed a worsening of sleep upon discontinuation of temazepam.[4,5,12] However, Dalmane patients showed no worsening of sleep after discontinuation,[4] a benefit that can help you achieve your ultimate therapeutic goal—untroubled and unaided sleep.

References: **1.** Karacan I *et al: Soc Sci Med 10*:239-243, May 1976. **2.** Bixler EO *et al: Am J Psychiatry 136*:1257-1262, Oct 1979. **3.** National Institute on Drug Abuse, U.S. Dept. Health, Education, and Welfare: *Sedative-Hypnotic Drugs: Risks and Benefits*, edited by Cooper JR; Rockville, MD, 1977. **4.** Kales A *et al: J Clin Pharmacol 17*:207-213, Apr 1977, and Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **5.** Bixler EO *et al: J Clin Pharmacol 18*:110-118, Feb-Mar 1978. **6.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **7.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **10.** Kales A *et al: JAMA 241*:1692-1695, Apr 20, 1979. **11.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 15, 1978. **12.** Mitler MM *et al: Br J Clin Pharmacol 8* (1):63S-68S, 1979.

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

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- Details of the acquired immunoregulatory disorder including clinical and **in vitro** characterization of the defects in cell mediated immunity, possible role of circulating immune complexes and HLA alloantigens.
- Epidemiologic investigations aimed at defining the causes of this outbreak in homosexual men; the possible roles of changing lifestyles, use of "recreational" drugs and sexually transmitted diseases.
- The spectrum of opportunistic infections, such as **Pneumocystis carinii** pneumonia, cytomegalovirus, Epstein-Barr virus, cryptococcosis and atypical Mycobacterium: The potential role of viruses as the causative agent of the immunologic disorder.
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VOLUME 137 • NUMBER 2 **AUGUST 1982**

TABLE OF CONTENTS

87 *Acute Cholecystitis: The Diagnostic Role for Current Imaging Tests*
GERBAIL T. KRISHNAMURTHY, MD
From the Nuclear Medicine and Research Services, Veterans Administration Medical Center, and the Departments of Clinical Pathology (Nuclear Medicine) and Medicine, The Oregon Health Sciences University, Portland.

95 *Urology/Sexualty Clinic: Results of Counseling of 67 Men*
ALEX L. FINKLE, PhD, MD, and SHIRLEY JACKSON
From the Department of Urology, University of California, San Francisco, School of Medicine.

MEDICAL PROGRESS
99 *The Differential Diagnosis of Pleural Effusions* STEVEN A. SAHN, MD
From the Division of Pulmonary Sciences, Department of Medicine, Pleural Space Laboratory, Webb-Waring Lung Institute, University of Colorado Health Sciences Center, Denver.

MEDICAL STAFF CONFERENCE
109 *Rheumatoid Arthritis—From Rubens to Restriction Maps* Chief Discussant: JOHN D. STOBO, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

IMPORTANT ADVANCES IN CLINICAL MEDICINE
Allergy—Epitomes of Progress
Items of progress in allergy. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

116 *Aspirin Desensitization in Rhinosinusitis Asthma* DONALD D. STEVENSON, MD
117 *Exercise-Induced Anaphylaxis* ABBA I. TERR, MD
117 *Standardization of Allergens* HAROLD BAER, PhD
118 *Immunologic Benefits of Breast Feeding* AUDREY J. NAYLOR, MD, DrPH
118 *Monoclonal Antibodies* RICHARD D. O'CONNOR, MD
119 *Immunoglobulin Subclass IgG4 Deficiency* DOUGLAS C. HEINER, MD, PhD
120 *Metabisulfite Sensitivity as a Cause of Asthma* SHERWIN A. GILLMAN, MD
121 *Urticarial Vasculitis*
JOHN G. CURD, MD; WILLIAM L. LUMRY, MD; DONALD D. STEVENSON, MD, and DAVID A. MATHISON, MD
121 *Rhinitis* ELI O. MELTZER, MD, and ALFREDO A. JALOWAYSKI, PhD
122 *Seminal Fluid Allergy* OSCAR L. FRICK, MD, PhD

EDITORIALS
124 WJM *Welcomes WMS*
124 *Further Comments on Pleural Effusions* GENNARO M. TISI, MD
Dr. Tisi is Associate Professor of Medicine, University of California, San Diego, School of Medicine; and Chief, Pulmonary Section, Veterans Administration Medical Center, San Diego.

125 *Tobacco and Cancer* JOHN H. HOLBROOK, MD
Dr. Holbrook is Associate Professor of Internal Medicine, University of Utah Medical Center, Salt Lake City.

126 *The AMA and a National Health Policy*
127 *Some Economic and Human Aspects of Cost Control in Patient Care*
PAUL J. SANAZARO, MD
Dr. Sanazaro, Berkeley, California, a member of the Editorial Board, is Consulting Editor for Medical Services and Health Care.

128 *Don't Kid Around* THOMAS K. HUNT, MD
From the Department of Surgery, University of California, San Francisco. Dr. Hunt is President of the American Trauma Society.

129 *On Having Encounters With Patients*

(Continued on Page 11)

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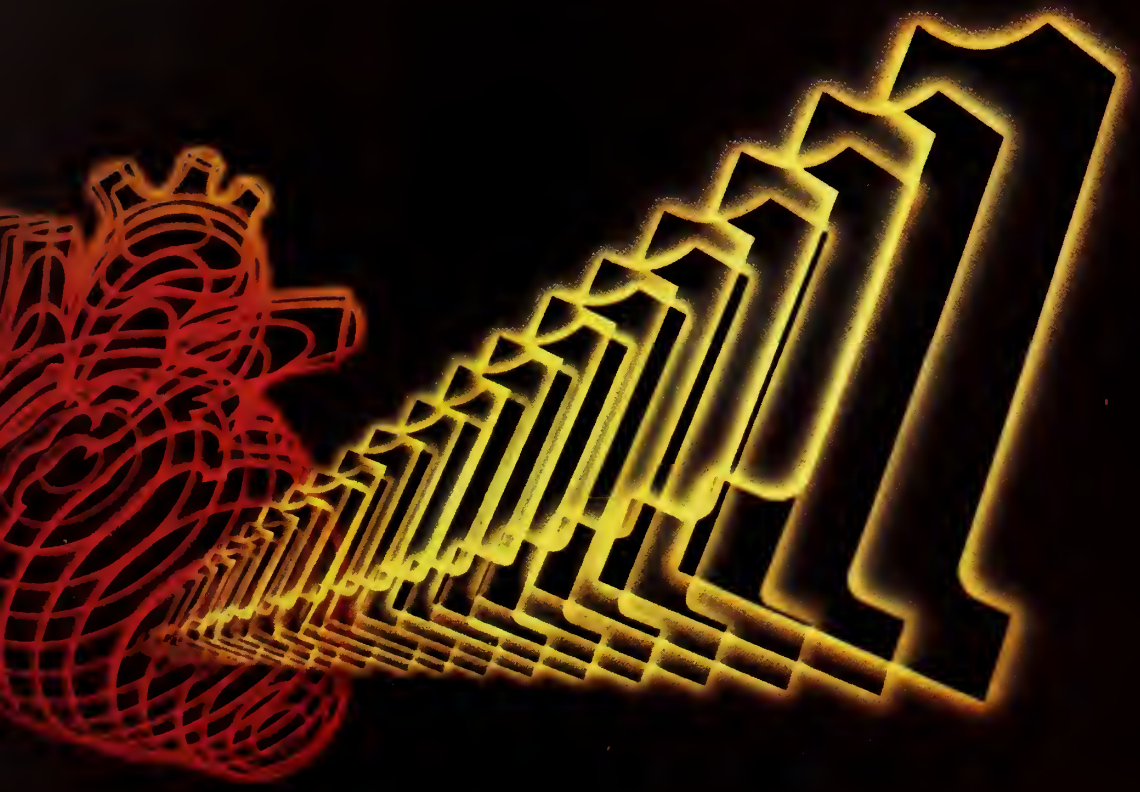

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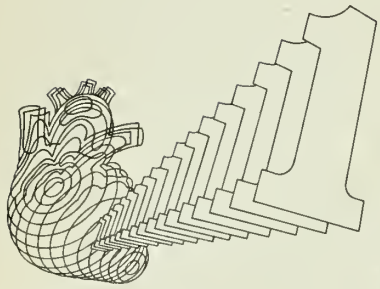

CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets
DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1(mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.
HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

SQUIBB

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(Continued from Page 7)

CASE REPORTS

130 *Association of Myoglobinuria With Adenovirus Infection*
HOOSHANG MESHKINPOUR, MD, and N. D. VAZIRI, MD
From the Department of Medicine, Divisions of Gastroenterology and Nephrology, University of California Irvine Medical Center, Orange, California.

132 *Polyarthritis Associated With Breast Carcinoma*
MICHAEL KWOK L. CHAN, MD; CHARLES S. HENDRICKSON, MD, and KATHLEEN E. TAYLOR, MD
From the Departments of Medicine, Kaiser-Permanente Medical Center, San Francisco, and Stanford University Medical Center, Stanford, California.

134 *Metaldehyde Poisoning From Slug Bait Ingestion*
W. T. LONGSTRETH, Jr, MD, and DAVID J. PIERSON, MD
From the Department of Medicine, Divisions of Neurology and Respiratory Disease, Harborview Medical Center, Seattle.

CORRESPONDENCE

138 *How Much Testing Is Needed?* RALPH C. JUNG, MD

138 *Sickling Crises at High Altitudes* PREETHAM KONDLAPOODI, MD

139 *Diagnosis of Testicular Torsion* BRUCE HAYNES, MD

139 *Holistic Medicine: Advances and Shortcomings* EDWARD SHAPIRO, MD

140 *Thrombotic Thrombocytopenic Purpura* GERALD P. SHELDON, MD

140 *Needle in the Foot* LAWRENCE H. WANETICK, MD, and RICHARD HILL, MD

TOPICS IN PRIMARY CARE MEDICINE

141 *Infectious Mononucleosis* MAXINE A. PAPADAKIS, MD
From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

SPECIAL ARTICLE

145 *The Costs and Risks of Medical Care—An Annotated Bibliography for Clinicians and Educators*
STEPHEN J. McPHEE, MD; LOIS P. MYERS, MPP, and STEVEN A. SCHROEDER, MD
From the Division of General Internal Medicine, Department of Medicine, and the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.

PREVENTIVE MEDICINE

162 *Infant Passenger Safety Education in Perinatal Services in California*
ALBERT CHANG, MD, MPH, and ESTHER LEVY, MS
From the California Center for Child Passenger Safety and the Division of Population, Family and International Health, UCLA School of Public Health, Los Angeles.

INFORMATION

166 *'Loads' Alert* ALI M. KHAJAWALL, MD; JOHN J. SRAMEK, Jr, PharmD, and GEORGE M. SIMPSON, MD
From the Drug Abuse Program, Metropolitan State Hospital, Norwalk, California, and the Department of Psychiatry and Behavioral Sciences, University of Southern California School of Medicine, Los Angeles.

169 *The Bedside Sherlock Holmes* FAITH T. FITZGERALD, MD, and LAWRENCE M. TIERNEY, Jr, MD
From the Departments of Medicine, University of California, Davis, School of Medicine, and the University of California, San Francisco, School of Medicine.

176 *In Memoriam*

178 *Announcement of the 87th Annual Meeting of the Utah State Medical Association, Salt Lake City, September 16 and 17, 1982*

BOOK REVIEWS

180 *Fetal Heart Rate Monitoring*
By ROGER K. FREEMAN, MD, and THOMAS J. GARITE, MD
Reviewed by NEIL K. KOCHENOUR, MD

180 *Drug Treatment—Principles and Practice of Clinical Pharmacology and Therapeutics—Second Edition*
Edited by GRAEME S. AVERY
Reviewed by LARRY WHEELER, PhD

Subscription Information, See Advertising Page 36

Books Received, See Advertising Page 46

Information for Authors, See Advertising Page 54

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An added complication... in the treatment of bacterial bronchitis*

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly)

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor* (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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August 16-20—**Advanced Diving Medicine.** UCSF at San Diego. Monday-Friday.

August 20-22—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $245. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

August 21-22—**Hemodynamic Monitoring/Pulmonary Artery Catheterization—Hands-on Workshops.** Calif. Soc. of Anesthesiologists at Stanford. Saturday-Sunday. 15 hrs. $275, members; $325, nonmembers. Contact: CSA, Ed. Prog. Div., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

August 21-22—**Office Orthopedics for the Internist and Family Practitioner.** UCLA. Saturday-Sunday. 12 hrs. $200.

August 22-24—**Evaluation and Management of Allergic and Asthmatic Diseases of Adults and Children.** UCD at Hyatt Del Monte, Monterey. Sunday-Tuesday. 16 hrs. $175.

August 23-September 3—**Intensive Residency in Occupational Medicine, Session I.** UCSF at Golden Gateway Holiday Inn, San Francisco. 12 days. 80 hrs. $1,000.

August 26-28—**Advances in Diagnostic Imaging.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. 20½ hrs. $275.

August 29-September 3—**Family Practice Refresher Course.** UCD at Hyatt Del Monte, Monterey. Sunday-Friday.

August 30-September 1—**Napa Valley Radiology Conference.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Napa Valley. Monday-Wednesday. 18 hrs. $275. Contact: Michael H. Reid, PhD, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

August 30-September 4—**5th Comprehensive Nephrology Review Course.** UCLA at Marriott, Los Angeles. Monday-Saturday. 38½ hrs. $595.

September 1—**Sports Medicine Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

September 8—**Current Concepts in Menopausal and Post-Menopausal Care.** LLU. Wednesday.

September 9-12—**Pediatric Urology.** UCD at Silverado, Napa Valley. Thursday-Sunday. 14 hrs. $225.

September 10-11—**Pediatric Emergency Medicine.** UCLA. Friday-Saturday. 14½ hrs. $180.

September 11—**9th Annual Radiology Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Beverly Hilton, Beverly Hills. Saturday. Contact: Doris McMath, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 12-25—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

September 13-15—**Gynecologic Laser Surgery and Colposcopy.** Robert Scott Med. Fndn., Pacific Inst. for Laser and Advanced Med. Technology, and Doctors' Hosp. of Montclair at Miramar-Sheraton, Santa Monica. Monday-Wednesday. 20 hrs. $550. Contact: Robert S. Scott, MD, 11600 Wilshire Blvd., Suite 400, Los Angeles 90025. (213) 478-3042.

September 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium I.** UCSD at Vacation Village, San Diego. Monday-Friday. 33 hrs. $425.

September 16-18—**4th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Thursday-Saturday.

September 20-22—**Alcoholism Treatment, Cooperation or Competition.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059 (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

September 20-24—**7th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Marriott, Maui. Monday-Friday. 21 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

September 21-22—**American Heart Association-Greater Los Angeles Affiliate—50th Anniversary Fall Symposium.** Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $70. Contact: Marilyn Cowan, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 24—**Advances in Transplantation—15th Annual Symposium on Renal Disease.** National Kidney Foundation of No. Calif. at Stanford. Friday. 6 hrs. $80. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd, Burlingame 94010. (415) 697-0110.

September 24-25—**Toxicology for Occupational Health Personnel.** PMC at Miyako Hotel, San Francisco. Friday-Saturday.

September 24-25—**Antigens and Immunotherapy: Present and Future.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott, Newport Beach. Friday-Saturday. Contact: Warren Richards, MD, Allergy-Clinical Immunology Div., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054.

September 24-25—**Update in Internal Medicine—27th Annual Medical Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Century Plaza, Los Angeles. Friday-Saturday. Contact: Mark Anthony, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 24-25—**Sexual Issues in Medical Office Practice.** UCSF. Friday-Saturday. 10½ hrs. $125. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

September 24-26—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

September 25—**Cancer and the Environment.** San Francisco Regional Cancer Fndn.; French Hosp. Med. Ctr.; Am. Cancer Soc., S.F. Unit, at French Hospital, San Francisco. Saturday. 4 hrs. Contact: Cecilia Cotter, S.F. Reg. Cancer Fndn., Bldg. 1805, San Francisco 94129. (415) 221-2132.

September 25—**Do's and Don'ts With Diets and Drugs.** UCLA. Saturday. 7 hrs. $90.

September 25—**What's New in Infectious Diseases.** Hospital of the Good Samaritan at Le Baron Hotel, San Jose. Saturday. 7 hrs. $40. Contact: Janice Grogan, Med. Ed., Hosp. of the Good Samaritan, 2425 Samaritan Dr., San Jose 95124. (408) 559-2457.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 25-October 3—**2nd Annual Recognition and Management of Diving Casualties.** UCSD at Sheraton Island Marina Inn, San Diego. 9 days. 60 hrs. Contact: Shirley Kolkey, Medicine, Education and Research Fndn., P.O. Box 81344, San Diego 92138.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: Registrar, ACEP, P.O. Box 61911, Dallas 75261. (214) 659-0911.

September 29-30—**39th Annual Brennemann Memorial Lectures.** L.A. Pediatric Soc. at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. $400. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

September 29-October 2—**Reconstructive Surgery of the Shoulder, Elbow, Hip and Knee: An In-Depth Course and Workshop.** UCLA. Wednesday-Saturday. 30 hrs. $450.

September 30-October 2—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

September 30-October 2—**Pulmonary Update.** UCSF. Thursday-Saturday.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Ctr., Torrance 90509. (213) 533-2233.

October 1-2—**Frontiers in Medicine: Implications for the Future.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. 16 hrs. $225.

October 1-2—**Intraocular Lens Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 1-2—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-7813.

October 1-2—**Pediatrics With Sydney Gellis.** UCD at Red Lion Inn, Sacramento. Friday-Saturday. 10 hrs. $95.

October 1-3—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 1-3—**Recent Advances in Anesthesia.** Anesthesiology Educational Fndn. at Holiday Inn, Monterey. Friday-Sunday. 10½ hrs. $200. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 2—**Flexible Fiberoptic Sigmoidoscopy, II.** Herrick Hospital and Health Center at Holiday Inn, Emeryville. Saturday. 7 hrs. $100. Contact: Lloyd C. Patterson, MD, Dir. of Med. Ed., Herrick Hosp. and Health Ctr., 2001 Dwight Way, Berkeley 94704. (415) 540-4546.

October 2—**5th Annual Heart Symposium.** Northridge Hospital Medical Center at Century Plaza, Los Angeles. Saturday. Contact: Sandra Rozzen, Northridge Hosp. Med. Ctr., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

October 2—**Gynecology Oncology Conference.** Sutter Community Hospitals at Hotel El Rancho, Sacramento. Saturday. 7 hrs. Contact: Gail Catlin, Oncology Coordinator, Sutter Mem. Hosp., 52nd and F Sts., Sacramento 94819. (916) 454-3333, ext. 1298.

October 2—**TMJ: What Is It and What To Do About It.** Scripps Clinic and Research Fndn. at Hilton, San Diego. Saturday. 6 hrs. $90. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 2-3—**The Skin from A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Saturday-Sunday.

October 3-6—**Controversies and Recent Advances in Pulmonary Medicine.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday. 17 hrs. $225. Contact: Karen L. Dutkowski, UCSF, Fresno-Central San Joaquin Valley Med. Ed. Prog., 2615 E. Clinton, Fresno 93703. (209) 224-3235.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Sci. Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 4-7—**Practical Electrocardiography—ECG Course for**

(Continued from Page 19)

Lo/Ovral Policy

A Policy of Extra-Low Dose Oral Contraception

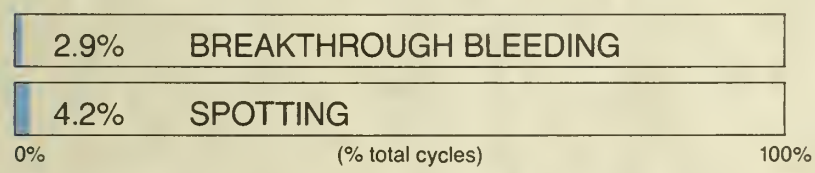
BENEFIT #1: EXTRA-LOW DOSE

The dosage is lower than "low." Lo/Ovral® contains an "extra-low" total hormone dose—30 mcg ethinyl estradiol and just 0.3 mg norgestrel. Even at this extra-low dose there was no reduction in contraceptive effectiveness. Nor any overall increase in breakthrough bleeding.*

BENEFIT #2: EARLY CYCLE BREAKTHROUGH PROTECTION

Lo/Ovral® offers your patients protection against breakthrough bleeding and spotting when they need it most—in the early cycles.* That's when they're usually most vulnerable to intermenstrual bleeding.

And in clinical trials totalling 22,489 cycles Lo/Ovral achieved a near-spotless record.* Just look below.



Cycle 1— 8.8%
Cycle 3— 3.3%

Cycle 1—10.6%
Cycle 3— 6.3%

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.

See full prescribing information.

SEE IMPORTANT INFORMATION ON FOLLOWING PAGE.

EXTRA-LOW DOSE LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

Oral contraceptive with a near-spotless record.

Wyeth Laboratories
Philadelphia, PA 19101

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IN BRIEF:
Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.
Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.
Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.
CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.
MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent.
RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.
ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.
2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.
3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.
4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.
5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.
6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.
7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.
8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.
9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.
10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.
11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.
12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.
Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.
2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.
3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.
4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.
6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.
7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.
8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.
9. The pathologist should be advised of OC therapy when relevant specimens are submitted.
10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.
Information for the Patient—See Patient Package Labeling.
Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.
Carcinogenesis—See Warnings on carcinogenic potential of OC's.
Pregnancy—Category X. See Contraindications, Warnings.
Nursing Mothers—See Warnings.
Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.
The following adverse reactions have been reported in patients on OC's and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening); intolerance to contact lenses.
The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.
Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.
Wyeth Laboratories, Phila., Pa. 19101

(Continued from Page 16)

Primary Physicians. Memorial Hospital Medical Center of Long Beach at Caesar's Palace, Las Vegas. Monday-Thursday. 14 hrs. $225. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 4-9—**Review Course in Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center of Long Beach at Sheraton Newport, Newport Beach. Monday-Saturday. 48 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 7-8—**52nd Annual Physicians' Postgraduate Symposium on Cardiovascular Diseases.** American Heart Assn., San Francisco Chap., at San Franciscan Hotel, San Francisco. Thursday-Friday. 11 hrs. Contact: Ms. Kari Olila, AHA, S.F. Chap., 421 Powell St., San Francisco 94102. (415) 433-2273.

October 7-9—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. $275.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 9—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hosp. Medical Ctr.-UCI Ctr. for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 9-10—**Update on Bone and Calcium.** UCSF. Saturday-Sunday.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Soc. at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 29 hrs.

October 9-17—**7th Annual International Body Imaging Conference.** West Park Hospital at Sheraton Royal Waikoloa Hotel, Kona, Hawaii. One week. 28 hrs. $385. Contact: Conf. Sec., Dept. of Radiology, West Park Hosp., 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 280.

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. 30 hrs. Contact: Geri Goodenough, Office of Sci. Mtgs., APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 10-15—**Annual Meeting of American Society of Plastic and Reconstructive Surgeons, Plastic Surgery Educational Foundation, and American Society of Maxillofacial Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. Contact: Linda Campbell, Mtg. Dept., ASPRS, 233 N. Michigan Ave., Suite 1900, Chicago 60601. (312) 856-1818.

October 10-15—**Reproductive Health Care: Changing Concepts in Fertility Regulation.** Wayne State Univ. at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ. Sch. of Med., Med. Research Bldg., Rm. 416, 5500 E. Canfield, Detroit 48201. (313) 577-1011.

October 11-13—**6th Annual Cancer Symposium.** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, Mtg. Coordinator, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 11-15—**Emergency Medicine.** USC. Monday-Friday.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

October 11-15—**12th Annual Review Course in Gynecology and Obstetrics.** USC at Hilton, Pasadena. Monday-Friday. 35 hrs. $450.

October 13—**Post-Operative Complications—Their Prevention and Management.** LLU. Wednesday. 4 hrs.

October 13—**12th Annual Respiratory Medicine Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

October 14-16—**Western Society of Allergy and Immunology—21st Annual Scientific Session.** Hyatt at Union Square, San Francisco. Thursday-Saturday. Contact: Joyce M. Gullixson, Exec. Sec., 1700 S.W. Columbia, Portland 97201. (503) 224-6159.

October 14-16—**Workshops in Clinical Hypnosis.** UCSD at Hanalei Hotel, San Diego. Thursday-Saturday. 21 hours. $310.

October 14-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

October 15-17—**Neurolinguistic Programming: Sex and Couples Therapy.** Institute of Sexual Behavior and Institute for Medical Education and Research at Village Inn, La Jolla. Friday-Sunday. 18 hrs. $200. Contact: Inst. of Sexual Behavior, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 15-17—**Substance Abuse Prevention Through Effective Parenting.** Isla Vista Health Projects, Inc., and San Diego State Univ. Student Health Services at Village Inn, La Jolla. Friday-Sunday. $150. Contact: Parenting, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 16—**Review Course for Gynecologic Pathology.** USC at Hilton, Pasadena. Saturday. 6 hrs. $75.

October 16-17—**Thyroid Today—1982, A Clinical Update for the Practicing Physician, First Annual Symposium.** Cypress Foundation at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $130. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

October 16-17—**Medical Psychiatry.** UCSF. Saturday-Sunday. 12½ hrs. $115 before October 1; $135, thereafter. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus, Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 17-19—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn, Napa. Sunday-Tuesday. 12 hrs. $180.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

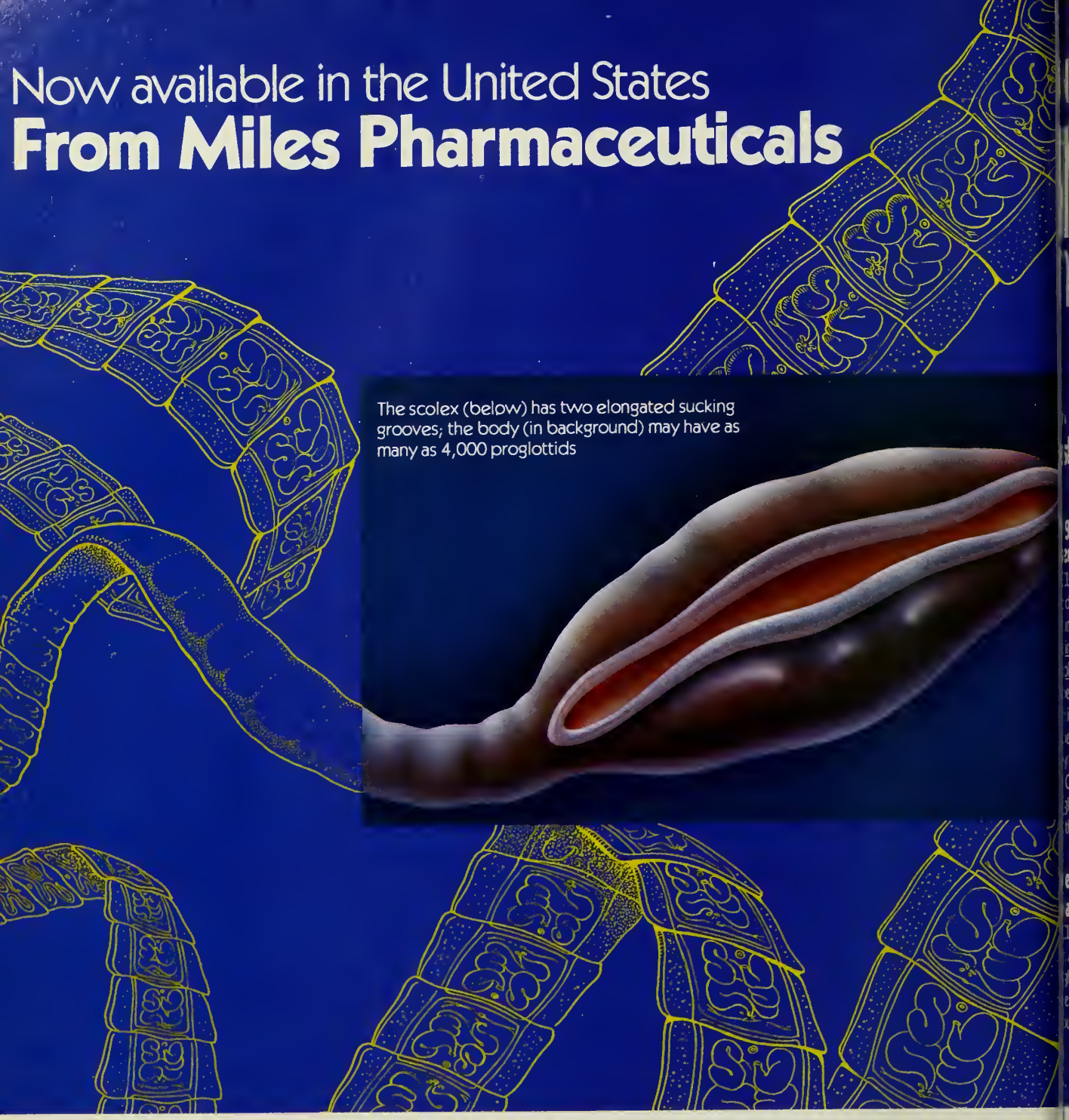
October 20—**New Concepts in Diabetes.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 21-24—**International Symposium on the Mitral Valve.** Scripps Clinic and Research Fndn. at Hotel del Coronado, Coronado. Thursday-Sunday. 23 hrs. $350. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

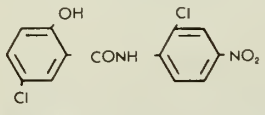
(Continued on Page 23)

Now available in the United States
From Miles Pharmaceuticals



The scolex (below) has two elongated sucking grooves; the body (in background) may have as many as 4,000 proglottids

DESCRIPTION: NICLOCIDE (niclosamide) is an anthelmintic provided in chewable tablet form at a strength of 500 mg per tablet. Niclosamide is 2', 5-Dichloro-4'-nitrosalicylanilide. The empirical formula is $C_{13}H_8Cl_2N_2O_4$ with the following structural formula.



CLINICAL PHARMACOLOGY: NICLOCIDE inhibits oxidative phosphorylation in the mitochondria of cestodes. Both in vitro and in vivo, the scolex and proximal segments are killed on contact with the drug. The scolex of the tapeworm, loosened from the gut wall, may be digested in the intestine, and thus may not be identified in the feces even after extensive purging. The use of NICLOCIDE has not been associated with the development of anemia, leukopenia or thrombocytopenia nor have there been any effects on normal renal and hepatic functions.

INDICATIONS AND USAGE: NICLOCIDE (niclosamide) is indicated for the treatment of tapeworm infections by Taenia saginata (beef tapeworm), Diphyllobothrium latum (fish tapeworm) and Hymenolepis nana (dwarf tapeworm).

CONTRAINDICATIONS: NICLOCIDE™ Tablets are contraindicated in individuals who have shown hypersensitivity to any of its components.

PRECAUTIONS: NICLOCIDE affects the cestodes of the intestine only. It is without effect in cysticercosis.

Drug Interactions: No data are available regarding interaction of niclosamide with other drugs.

Carcinogenesis, Mutagenesis, Impairment of fertility:

Carcinogenicity Potential: Although carcinogenicity studies on niclosamide per se have not been done, long-term feeding studies on its ethanolamine salt in rats and mice did not show carcinogenicity. Mutagenicity tests have not been performed.

Pregnancy: Pregnancy Category B: Reproduction studies in rabbits and rats at doses of 25 times the human therapeutic dose and in mice at 12 times the human therapeutic dose, have revealed no evidence of impaired fertility or harm to the fetus due to niclosamide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed.

Nursing Mothers: No studies are available.

Pediatric Use: In children under 2 years of age, the safety of the drug has not been established.

ADVERSE REACTIONS: The incidence of side effects has been reported as follows: nausea/vomiting 4.1%, abdominal discomfort including loss of appetite 3.4%, diarrhea 1.6%, drowsiness, dizziness, and/or headache 1.4%, and skin rash including pruritus ani 0.3%. Other side effects listed in decreasing order of frequency were: oral irritation, fever, rectal bleeding, weakness, bad taste in mouth, sweating, palpitations, constipation, alopecia, edema of an arm, backache and irritability. There was also one instance of a transient rise in SGOT in an i.v. narcotic addict. Two cases of urticaria reported may be related to the breakdown products of the tapeworm. Al effects were mild or moderate and transitory and dic necessitate discontinuation of the treatment.

OVERDOSAGE: Insufficient data are available. In the eve overdose a fast-acting laxative and enema should be s Vomiting should not be induced.

DOSAGE AND ADMINISTRATION:

1. Taenia saginata and Diphyllobothrium latum
   a. Adults: 4 tablets (2.0 g) chewed thoroughly in a s dose.
   b. Children weighing more than 34 kg (75 lbs): 3 ta (1.5 g) chewed thoroughly in a single dose.
   c. Children weighing between 11 and 34 kg (25 t lbs): 2 tablets (1.0 g) chewed thoroughly in a single
2. Hymenolepis nana
   a. Adults: 4 tablets (2.0 g) chewed thoroughly as a daily dose for 7 days.
   b. Children weighing more than 34 kg (75 lbs): 3 ta (1.5 g) chewed thoroughly on the first day, th tablets (1.0 g) daily for next 6 days.
   c. Children weighing between 11 and 34 kg (25 to 75 l tablets (1.0 g) to be chewed thoroughly on the firs then one tablet (0.5 g) daily for next 6 days.

   T. saginata and D. latum infections are usually du single adult worm and require an intermediate h their life cycle. With Hymenolepis nana multiple i tions are the rule. No intermediate host is req both larval and adult stages of the worm may be f in the human intestine where the complete life occurs. Since the drug is more effective agains

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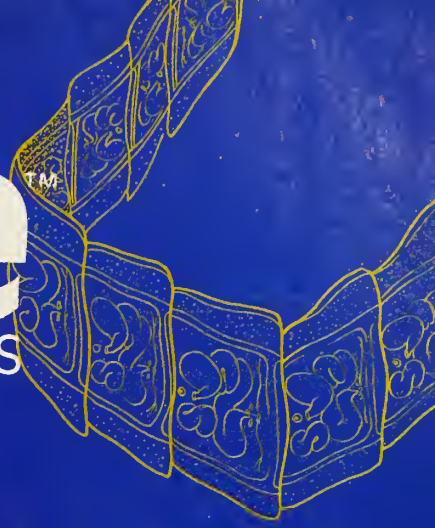
MLO

EW Prompt-Action

nICLOCIDE™

niclosamide chewable tablets 500 mg.



safe, reliable single-dose taeniacide that eradicates beef and h tapeworms in a single day

ghly effective prompt niacidal action

LOCIDE™ (niclosamide) is consid- d as the drug of choice in elimi- ng beef tapeworm (Taenia nata), fish or broad tapeworm hyllobothrium latum), and dwarf eworm (Hymenolepis nana) from ntestines. Except for the dwarf eworm, which requires a seven- treatment (SEE FULL PRESCRIBING ORMATION BELOW), a one-day e-dose treatment is sufficient to hese cestodes.

aks hold of head and in of segments

LOCIDE works promptly and sim- After tablets are chewed thor- nly and washed down with a water (for children tablets uld be pulverized and mixed with a little water), the insoluble micronized crystals act by direct contact on the tapeworm head. As soon as NICLOCIDE reaches the parasite, the scolex and upper segments are killed, thus depriving the whole chain of its hold. It is then discharged in stool either in one piece or smaller portions.*

Safe and well tolerated/ little gastrointestinal mucosa irritation

NICLOCIDE has proved exceptionally well accepted by adults as well as children weighing more than 11 Kg. (25 lbs.).

Convenient one-day single-dose administration†

NICLOCIDE Tablets are taken as a single dose after breakfast. Tablets must be chewed or pulverized thoroughly and washed down with a little water. No special diet or preparation is necessary except in patients who are constipated. In these cases, a thorough cleansing of the bowels may be required before treatment. The avoidance of alcohol during treatment is the only other requirement.

---

*A drastic saline purge, such as magnesium sulfate or sodium sulfate should be given two hours after the NICLOCIDE dose if it is required that the tapeworms be expelled rapidly and in one piece.

†In infections with beef tapeworm (T. saginata) and fish tapeworm (D. latum) one single dose is sufficient; for infections with dwarf tapeworms (H. nana) a seven-day treatment is recommended (SEE FULL PRESCRIBING INFORMATION ON THESE PAGES).

mature than the larval stage, therapy must be extended over several days to cover all stages of maturation.
Patients with H. nana must be instructed to observe strict personal and environmental hygiene to avoid autoinfection with this parasite.
NICLOCIDE™ must be thoroughly chewed and then swallowed with a little water. No special dietary restrictions are necessary before or after treatment. The best time to take the drug is after a light meal (e.g., breakfast).
A mild laxative may be desirable in constipated patients to achieve a normal bowel movement.
Young children should have the tablets crushed to a fine powder and mixed with a small amount of water to form a paste.
NICLOCIDE has a vanilla taste which is not unpleasant to most persons.
NICLOCIDE is suitable for administration on an ambulatory or outpatient basis.
4. Follow-up
As the vermicidal action of NICLOCIDE renders the tapeworm, especially the scolex and proximal segments, vulnerable to destruction during their passage through the gut, it is not always possible to identify the scolex in stools. The sooner the tapeworm is passed and examined after treatment, the better the chance of identification of the scolex. Segments and/or ova of beef or fish tapeworm may be present in the stool for up to 3 days after therapy. Persistent T. saginata or D. latum segments and/or ova on the seventh day post therapy indicate failure. A second identical course of treatment may be given at that time.
No patient should be considered cured unless the stool has been negative for a minimum of three months.

HOW SUPPLIED: NICLOCIDE is available as round, light yellow chewable tablets, scored on one side, embossed with the word Miles and number 721, each containing 500 mg of niclosamide, and is supplied in boxes of 4 tablets.
Storage Conditions: Store below 86°F (30°C), avoid freezing

Manufactured by
Bayvet Division Cutter Laboratories, Inc.
Shawnee, Kansas 66201

Distributed by:
Miles Pharmaceuticals
Division of Miles Laboratories, Inc.
West Haven, Connecticut 06516

PD100551 18612 Made and printed in USA April 1982

nICLOCIDE™

Drug of Choice for Eliminating Tapeworms

MILES
Miles Pharmaceuticals

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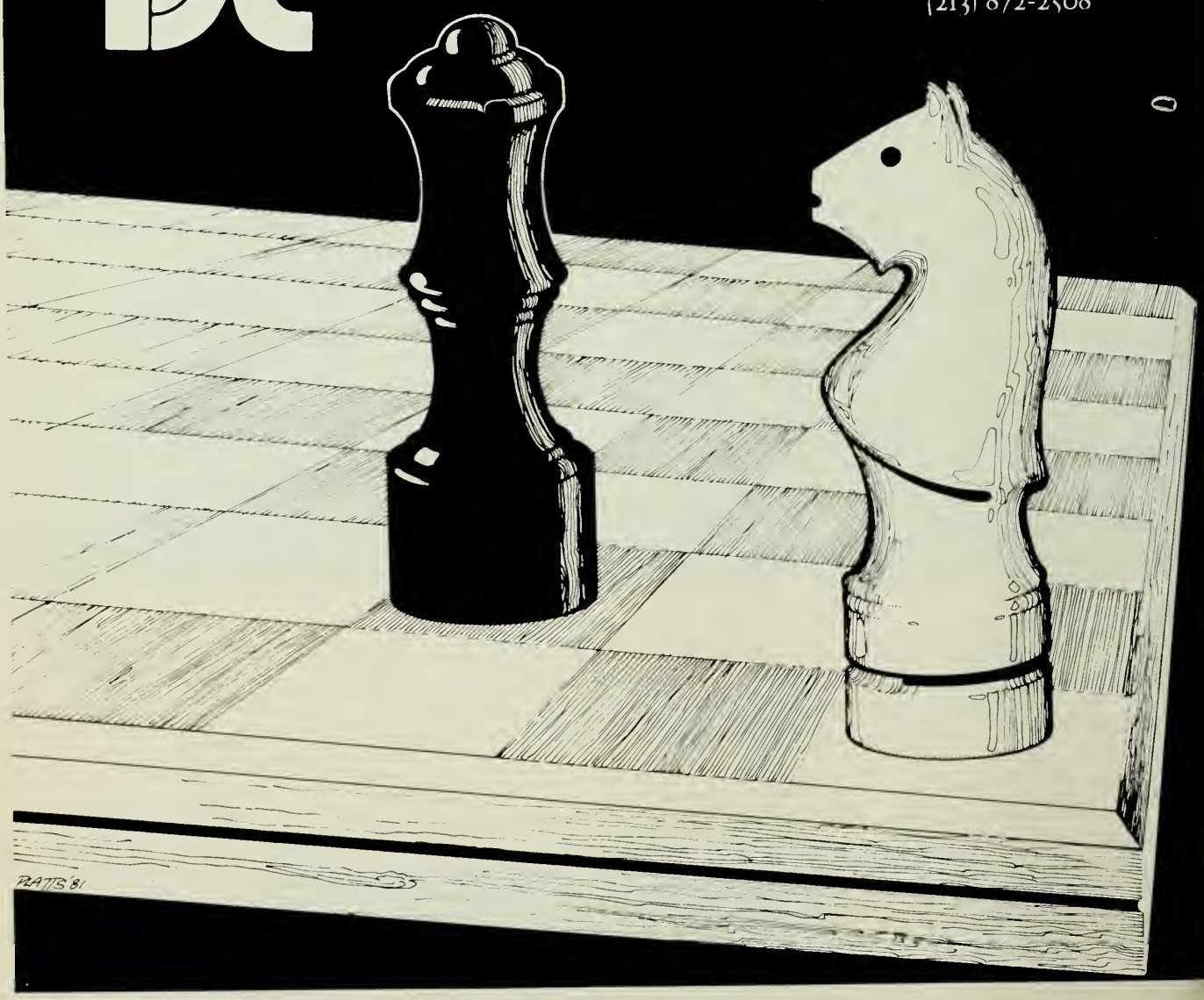

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October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 22-24—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $275. Contact: Howard D. Groveman, MD, UCSD School of Medicine (M-022), La Jolla 92093. (714) 452-4613.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

October 23—**Current Trends in Cardiovascular Therapy.** Cedars-Sinai Medical Center at Eisenhower Medical Center, Rancho Mirage. Saturday. 8 hrs. $40. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 23-24—**Western Occupational Health Conference—1982.** Western Occupational Medical Assn. at Travelodge at the Wharf, San Francisco. Saturday-Sunday. 10 hrs. $75, members; $95, nonmembers. Contact: WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 23-25—**OB and GYN Endocrinology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Monday.

October 23-30—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela. One week. 20 hrs. $275. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 24-25—**Meeting of International Strabismological Association and American Association of Pediatric Ophthalmology and Strabismus.** ISA, AAPOS and PMC at Asilomar, Pacific Grove. Sunday-Monday. Contact: PMC.

October 25-28—**7th Annual Family Practice Update.** LLU. Monday-Thursday. 29 hrs. $225.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

October 27-28—**Vitrectomy.** PMC. Wednesday-Thursday.

October 28-30—**Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 28-30—**2nd Bi-Annual Course in Lower Extremity Trauma: Treatment, Complications and Controversies.** Bone and Joint Disease Foundation at Vacation Village, San Diego. Thursday-Saturday. Contact: Lower Extremity Trauma, P.O. Box 9494, San Diego 92109. (714) 282-9316.

October 29-31—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sahara, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 30—**Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

October 30—**The Troubled Child: Four Practical Approaches.** Del Amo Hospital and American Academy of Pediatrics at Del Amo Hospital, Torrance. Saturday. 4 hrs. $25. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

October 30-November 5—**American Academy of Ophthalmology.** Moscone Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

November 1-3—**Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo Inn, San Diego. Monday-Wednesday. 19 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037.

November 1-4—**Interstate Postgraduate Medical Association—Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., IPMA, P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

November 4-5—**Centennial Sterling Bunnell Memorial Lectureship Program—Surgery of the Hand.** UCSF at Letterman Army Institute of Research, San Francisco. Thursday-Friday. 15 hrs. $250.

November 5-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 6—**The Sexually Active Adolescent—Implications for the Health Care Professional.** UCLA. Saturday. 7 hrs. $90.

November 6—**Four by George Vaillant: Natural History of Male Alcoholism; Hierarchy of Ego Mechanisms; Work as a Predictor of Mental Health; Case Conference.** Del Amo Hospital, Torrance. Saturday. 7 hrs. $50. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

November 6-7—**Blood Gas and Acid-Base Disorders.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-7—**Invasive Methods and Hemodynamic Monitoring.** STAN. Saturday-Sunday. 15 hrs. $325.

November 6-7—**Trauma.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-8—**Nutrition.** PMC and Institute for the Study of Human Knowledge at San Francisco. Saturday-Monday. Contact: PMC.

November 7-12—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui. Sunday-Friday. $350.

November 7-13—**Allergy and Immune Diseases.** Symposium Maui, Inc., and Hawaii Chap., AAFP, at Lahaina Resort, Kaanapali, Maui. One week. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, HI 96761.

November 10—**Pediatric Emergencies.** LLU. Wednesday. 4 hrs.

November 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

November 10-14—**Sports Medicine Now.** UCD at Hyatt Del Monte, Monterey. Wednesday-Sunday. 24 hrs. $275.

November 11-13—**Critical Decisions in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Thursday-Saturday. 12 hrs. $235. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 11-13—**First National Conference on Infantile Apnea and Home Monitoring of High Risk Infants.** Eisenhower Medical Center and Medical Center of Tarzana at Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: Annenberg Center for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 340-3911, ext. 1661.

November 11-14—**Controversial Areas in Surgery of the Head and Neck.** Institute for Medical Education and Research at Hilton Beach and Tennis Resort, San Diego. 20 hrs. $250. Contact: IMER, P.O. Box 9494, San Diego 92109. (714) 272-3126.

(Continued on Page 29)

A NEW AGE IN THE CONTROL OF ANGINA

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PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:
—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply
—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand
—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page.

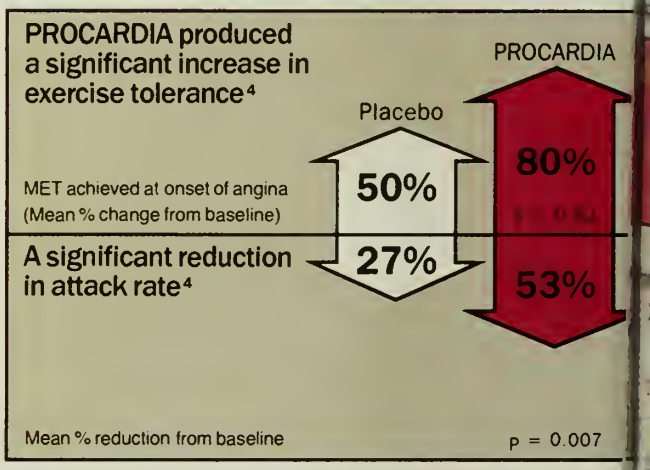
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy)



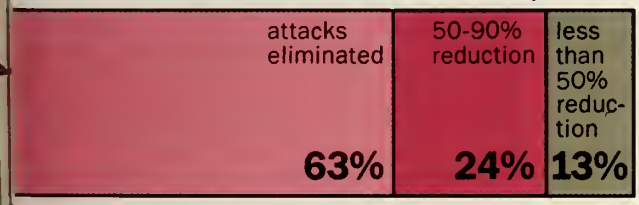
Double-blind, placebo-controlled, crossover 20-week stu of 32 patients (27 evaluated for attack rate; 19 for exer tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCARI has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exerci tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incompl

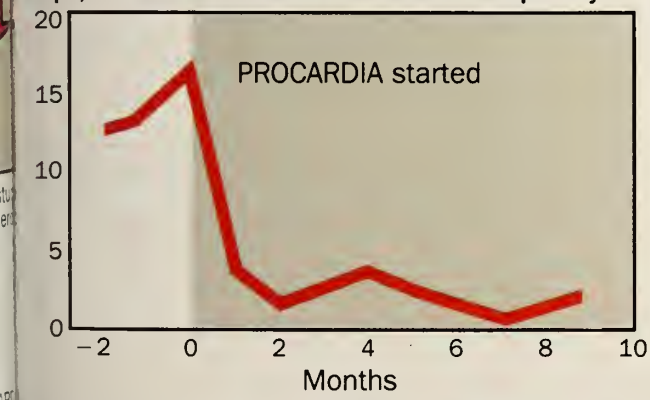
Please see PROCARDIA Brief Summary on last page.

ı vasospastic angina

ROCARDIA eliminated attacks in 63% of patients[5]

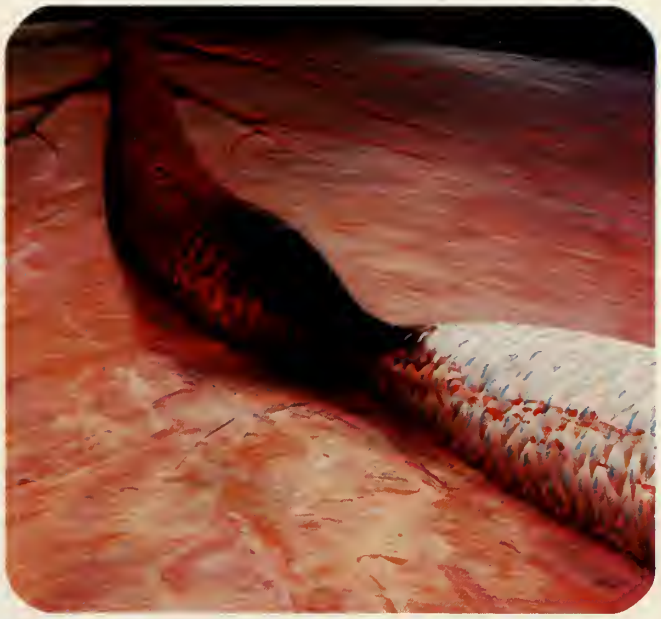


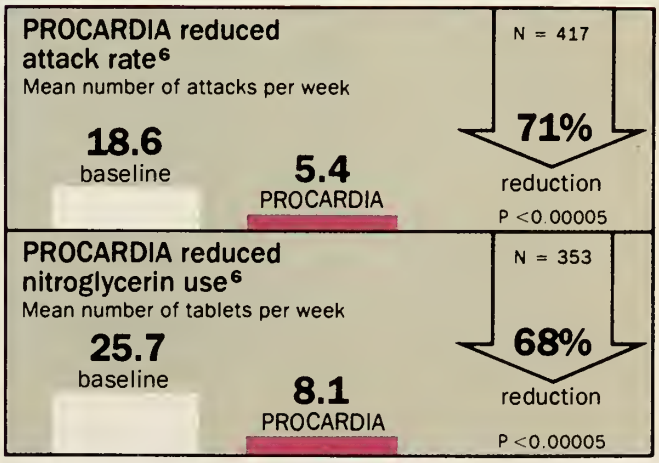
ompt, sustained decrease in attack frequency[5]



ıg-term, open study of 127 patients unresponsive to beta ckers and/or nitrates with symptoms of myocardial ıemia and demonstrated coronary artery spasm.)CARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)





Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

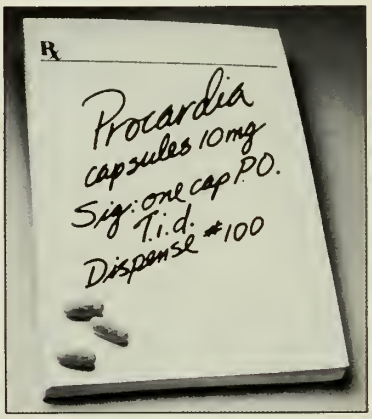
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d.*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

References

1. Lichtlen PR, Engel H-J, Wolf R, et al. Regional myocardial blood flow in patients with coronary artery disease after nifedipine. in Lichtlen PR, Kimura E, Taira N (eds). *International Adalat® Panel Discussion. New Experimental and Clinical Results.* Tokyo. Excerpta Medica. 1978. pp 69–85.
2. Maseri A, Chierchia S. Angina pectoris—a new dimension, a new approach. Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E. *Introduction. New Concepts in Ischemic Heart Disease. The Role of Coronary Artery Spasm.* New York. Science & Medicine, Inc. 1980. p 1.
4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator). Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology. Atlanta, Georgia, April 29, 1982.

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(nifedipine)

For Oral Use

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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(Continued from Page 23)

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS Omaha NE 68101. (402) 551-0801.

November 12-14—**28th Annual Group Therapy Symposium.** UCSF at Holiday Inn, Berkeley. Friday-Sunday. 18 hrs. $125. Contact: Aveleen Blumenstock, Asst. Dir., Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

November 13—**CT of the Spine.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Saturday. 6 hrs. $95. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049. Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 14—**The Lung in 1982.** Granada Hills Community Hospital and UCLA at Sheraton-Universal, North Hollywood. Sunday. Contact: Germaine Trasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

November 14-17—**California Academy of Family Physicians—Annual Meeting.** Hotel del Coronado Coronado. Sunday-Wednesday. Contact: CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

November 15-19—**An International Perspective on Substance Abuse: The Problem, Its Treatment, and Medical Education.** Assn. for Medical Education and Research in Substance Abuse; World Health Org.; State Univ. of NY Downstate Med. Ctr.; et al at Claremont Hotel, Oakland. Monday-Friday. Contact: Dr. Charles Buchwald, Downstate Med. Ctr., 450 Clarkson Ave.-Box 129, Brooklyn, NY 11203. (212) 270-3150.

November 17—**Controversies in the Management of Early Breast Cancer.** Hospital of the Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 19-22—**Pediatric Update.** Calif. Chapters, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 21-24—**Pacific Coast College Health Association—Annual Meeting.** PCCHA and San Diego State Univ., Student Health Services, at Hyatt Islandia, San Diego. Sunday-Wednesday. 14 hrs. $40, members; $50, nonmembers. Contact: David Bearman, MD, Student Health Services, San Diego State Univ., San Diego 92182. (714) 265-5281.

November 28-December 1—**Kids Have Bones, Too.** UCD at Hyatt Del Monte, Monterey. Sunday-Wednesday. 11 hrs.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 3-4—**The Anterior Cruciate Ligament "State of the Art."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 3-5—**Clinical Management of Coronary Disease and**

(Continued on Page 42)

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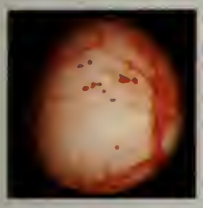

CLASSICAL INTERSTITIAL CYSTITIS

- ☐ irritative voiding symptoms
- ☐ suprapubic pain
- ☐ functional bladder capacity reduced
- ☐ anatomical bladder capacity:
  - EARLY — normal
  - CLASSICAL — reduced
- ☐ vesical mucosa:
  - EARLY — normal appearing
  - CLASSICAL — ulcerated, scarred
- ☐ submucosal vesical hemorrhages observed following second overdistension

DIAGNOSIS: INTERSTITIAL CYSTITIS

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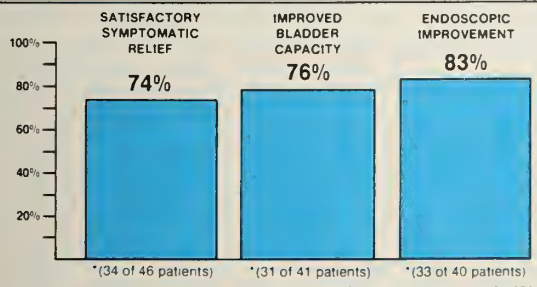
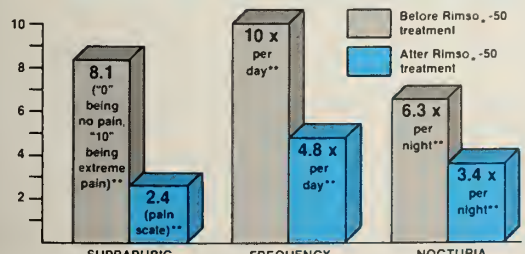


*STEWART, B H., et al., J. Urol., 36 116, 1976



** Data on File — Research Industries Corporation

FOR FURTHER INFORMATION

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Rimso®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE: Rimso®-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso®-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS: None known.

WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso®-50. The physician should be cognizant of this possibility in prescribing Rimso®-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso®-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso®-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide. The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION: Instillation of 50 ml of Rimso®-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of Rimso®-50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).

HOW SUPPLIED:
Bottles contain 50 ml of sterile and pyrogen-free Rimso®-50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (15° to 30° C).
Do not autoclave.
NDC #0433-0433-05

*Stewart, B H., et al., J. Urol., 36:116, 1976

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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THE WESTERN
Journal of Medicine

Refer to: Krishnamurthy GT: Acute cholecystitis: The diagnostic role for current imaging tests. West J Med 1982 Aug; 137:87-94

Acute Cholecystitis: The Diagnostic Role for Current Imaging Tests

GERBAIL T. KRISHNAMURTHY, MD, *Portland*

Acute cholecystitis is a relatively common clinical entity characterized histopathologically by obstruction of the cystic duct due to either edema or stone or both. Thorough clinical assessment and selection of the appropriate diagnostic tests are crucial in making an early diagnosis before surgical treatment. Many diagnostic tests are available for imaging the gallbladder. Hepatobiliary imaging using technetium Tc 99m IDA is the test of choice to either exclude or confirm the diagnosis of acute cholecystitis and it carries a discriminating power greater than that of cholecystography or ultrasonography. In most patients the exclusion of the diagnosis of acute cholecystitis can be made as early as 30 minutes and the confirmation within three hours. The confirmation of acute cholecystitis by radionuclide imaging obviates the need for either cholecystography or ultrasonography.

GALLBLADDER DISEASE is considered one of the nation's major medical problems.[1] Annually 500,000 cholecystectomies are done in the United States for either acute or chronic cholecystitis. Acute cholecystitis (AC) usually presents as an emergency in terms of both diagnostic urgency and therapeutic intervention and of course any delay in diagnosis further delays therapy. Immediate cholecystectomy is recommended as the proper therapy for acute cholecystitis on the basis that there is no evidence of increased operative mortality or morbidity associated with early cholecystectomy.[2-6] A recent *Lancet* editorial stated that "once the diagnosis has been confirmed the patient should be put on the next convenient operating list for cholecystectomy under antibiotic cover."[7] Such a measure is thought to reduce up to ten days the hospital stay for each patient, in contrast to conservative (late) cholecystectomy.[8,9] With these recent changing trends in management, attention has shifted toward the need for early diagnosis.

Clinical Assessment

A thorough clinical assessment and a high index of suspicion of AC are essential in any patient who presents with acute right upper quadrant pain and fever. Other clinical conditions that mimic AC include appendicitis, gastritis, pancreatitis, acute myocardial infarction, right lower lobe pneumonia and right renal colic. Fever, right upper quadrant pain and a positive Murphy's sign are well-established signs and symptoms of acute cholecystitis. In one study when the clinical prob-

From the Nuclear Medicine and Research Services, VA Medical Center, and Departments of Clinical Pathology (Nuclear Medicine) and Medicine, The Oregon Health Sciences University, Portland.

Submitted, revised, April 2, 1982.

This project was supported by the Veterans Administration.

Reprint requests to: G. T. Krishnamurthy, MD, Nuclear Medicine Service (115), VA Medical Center, PO Box 1034, Portland, OR 97201.

ABBREVIATION USED IN TEXT

AC = acute cholecystitis

ability was less than 50 percent, none of the patients with right upper quadrant pain and fever had AC. When the probability was between 51 percent and 99 percent, 16 of 33 patients (49 percent) had AC; and when the probability was between 90 percent and 99 percent, 10 of 13 patients (77 percent) had AC (Table 1). As 23 percent of patients with the highest clinical probability did not have AC, it is evident that a complete clinical examination alone cannot be relied on as the final indication for a surgical procedure.[10] Due to such a high false-positive fraction, it is necessary to confirm AC via other, primarily imaging, diagnostic tests.

The available imaging tests for detecting AC and their current costs (in Portland) are shown in Table 2. The results of most tests are usually evaluated in terms of sensitivity (also called true-positive ratio, which indicates the fraction of times the test findings are abnormal or positive in patients with AC) and specificity (also called true-negative ratio, which indicates the fraction of times the test findings are negative or normal in a group of persons without AC). As none of the imaging tests are perfect and sensitivity deals only with the ill population and specificity deals only with the well population, they do not enlighten on the more important question: What is the likelihood of AC being present when a test result is either positive (abnormal) or negative (normal)? To answer these questions, one has to take into account, in addition, the prevalence of the disease in the population under study and the false-negative (fraction of times the test results are normal in patients with AC) and false-positive (fraction of times the test results are abnormal in subjects without AC). Using these additional parameters, one can evaluate the true meaning of the test result in terms of likelihood of disease.

Imaging Techniques

Seven different types of noninvasive imaging tests are available for the detection of AC (Table 2). Depending on a physician's confidence and familiarity, he or she may decide to choose all of them or, more likely, a combination of a few. A plain x-ray film of the abdomen occasionally will show gallstones or a calcified gallbladder wall or ileus. Plain x-ray films do not show AC directly but are used primarily to detect changes accompanying AC.[11-13]

Cholecystography (Oral)

Since its introduction in 1924, cholecystography using contrast media given orally has been the standard diagnostic test for detecting gallbladder disease.[14] For the gallbladder to be visualized on

TABLE 1.—*Accuracy of Clinical Assessment in the Diagnosis of Acute Cholecystitis (AC)**

Clinical Probability of AC		No Acute Cholecystitis		Acute Cholecystitis	
Percent	(No. of patients)	Number	(percent)	Number	(percent)
10-49	(3)	3	(100)	..	..
50-99	(33)	17	(51)	16	(49)
90-99	(13)	3	(23)	10	(77)
10-99	(36)	20	(55)	16	(45)

*Reproduced with permission from Freitas et al.[10]

TABLE 2.—*Cost in Portland, Oregon, of Noninvasive Diagnostic Imaging Tests for Acute Cholecystitis*

Radiographic procedures	
Plain film of abdomen	$ 34
Cholecystography (oral)	73
Cholangiography (intravenous)	112
Tomography (infusion)	96
Computerized tomography of liver and gallbladder	397
Ultrasonography	122
Imaging using radionuclides technetium Tc 99m IDA	265
TOTAL	$1,099
Hospital bed cost per day	$ 195

TABLE 3.—*True-Positive, True-Negative, False-Positive and False-Negative Ratios of Imaging Tests for Acute Cholecystitis*

Test	True-positive (sensitivity) Percent	False-negative Percent	True-negative (specificity) Percent	False-positive Percent
Radionuclide imaging using technetium Tc 99m IDA[18,19,58,59]	95	5	94	6
Cholecystography (oral)[18-20]	75	25	82	18
Ultrasonography[18,46]	50	50	62	38

TABLE 4.—*Total Cost for Confirmation of the Diagnosis of Acute Cholecystitis in Portland, When Only Two Imaging Tests Are Used*

Plain x-ray film of abdomen	$ 34
Technetium Tc 99m IDA imaging	265
TOTAL	$299

the x-ray film, the bile should achieve iodine concentration of 0.25 to 1.0 grams per dl, which occurs between 14 and 19 hours after oral ingestion of the dye.[15-17] The average sensitivity and specificity of a cholecystogram in the diagnosis of AC are 75 percent and 82 percent, respectively (Table 3).[18-20]

Cholangiography using intravenous injection of contrast media depends very much on the functional integrity of the liver cells. The test is of value when the serum bilirubin level is normal and not reliable when the level exceeds 2 mg per dl.[21-27] Tomography following infusion of contrast media is based on the fact that an inflamed gallbladder wall in AC is thickened and concentrates the contrast media.[28-31] However, increased wall thickness has also been reported in patients without biliary disease.[32] The role of computerized tomography is not clearly established.[33-35]

Ultrasonography

Ultrasonography has been used in the past ten years with increasing frequency.[36-38] The reported accuracy of ultrasound studies for detecting gallstones ranges from 91 percent to 98 percent.[39,40] The echogenic features of all gallstones are similar; hence, ultrasonography cannot reliably differentiate stones in AC from those in chronic cystitis or "silent" (asymptomatic) gallstones. Gallbladder wall thickening is sometimes used as evidence for AC.[23,41-45] However, wall thickening is not specific for AC and is found in patients with hypoalbuminemia, ascites, 10 percent to 45 percent of patients with chronic cholecystitis or partially or completely contracted normal gallbladders[45-50] and in only about 45 percent of patients with AC.[46] When used in conjunction with imaging using radionuclides and with cholecystography on the same group of patients, the sensitivity and specificity of ultrasonography in the detection of AC are shown to be 50 percent and 62 percent, respectively.[18]

Radionuclide Biliary Imaging With Technetium Tc 99m IDA

There are now more than half a dozen agents available for radionuclide hepatobiliary imaging.[51-53] Structurally all are closely related to lidocaine and do not cause any physiologic changes on injection.[54] Because all of the agents work when the serum bilirubin level is normal, whereas only a few are useful at higher bilirubin levels, the selection of an individual agent should be based on the knowledge of serum bilirubin level.[55] Technetium Tc 99m paraisopropyl and parabutyl analogues are more resistant to displacement by bilirubin than dimethyl IDA.[56] The resistance is attributed to their greater protein-binding capacity, which reduces urinary and enhances hepatic excretion.[57]

In normal persons and in patients with normal serum bilirubin levels, the entire biliary system is usually visualized within an hour (Figure 1). In 48 normal volunteers studied in our department, the gallbladder was clearly seen, thus establishing

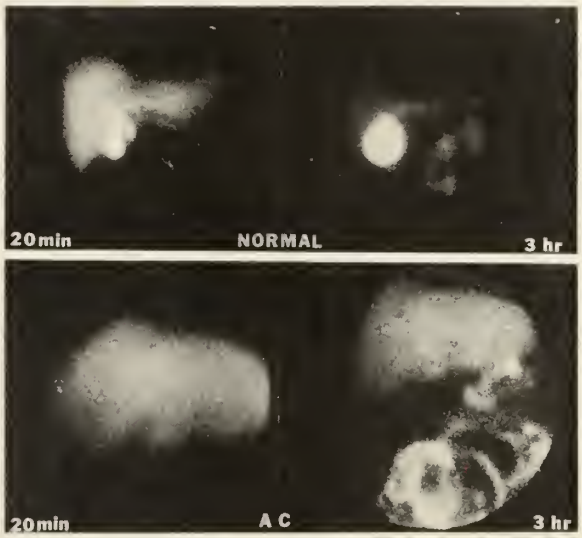

Figure 1.—Technetium TC 99m IDA biliary imaging study in a normal person and in a patient with acute cholecystitis (AC). Note gallbladder appearance at 20 minutes in the normal person and the nonappearance after three hours in the patient with AC.

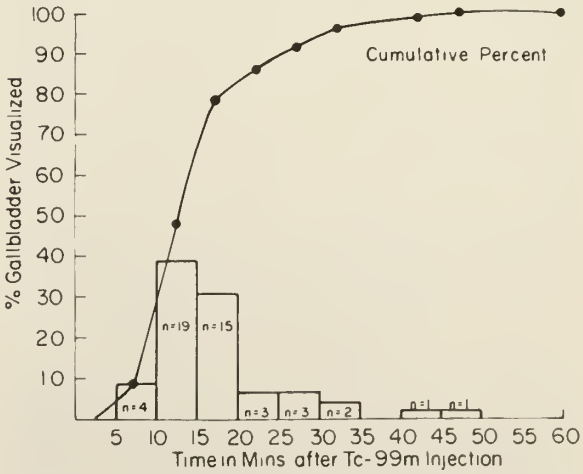

Figure 2.—The time (X axis) of appearance of the gallbladders (Y axis) in 48 normal volunteers following intravenous injection of technetium TC 99m IDA. The number of subjects at each interval is shown inside the column.

the patency of the cystic duct, in 50 percent of the subjects within 15 minutes, 80 percent within 20 minutes and 100 percent within 50 minutes (Figure 2). AC is diagnosed when the gallbladder is not seen (Figure 1). When the gallbladder is seen, the diagnosis of acute cholecystitis can be excluded within 20 minutes; however, the confirmation of the diagnosis requires imaging up to three to four hours. In some patients with chronic cholecystitis or cholelithiasis, or both, the gallbladder is often visualized after three to four hours. The average sensitivity and specificity of radionuclide imaging for AC (Table 3) are 95 percent and 94 percent, respectively.[18,58,59] Eight cases of false-negative hepatobiliary imaging studies with technetium Tc 99m IDA have been reported.[60,61]

Bayes' Analysis

The knowledge of sensitivity, specificity and false-negative and false-positive ratios is essential to compare the relative merits of the diagnostic methods. The optimum choice of sensitivity and specificity should ideally be drawn from analysis of the receiver operating characteristics (ROC) curve.[61] Because no single test can absolutely exclude or confirm AC, the final answer requires the application of bayesian analysis.[61,62] The probability of acute cholecystitis being present when the test result is positive or negative is determined by applying the following formula:

$$\text{probability of AC when test is positive (abnormal)} = \frac{(\text{sensitivity}) \times \text{prevalence of AC in study population}}{\text{sensitivity} \times \text{prevalence of AC in study population} + \text{false-positive fraction} \times \text{prevalence of no AC in study population}}$$

$$\text{probability of AC when test is negative (normal)} = \frac{\text{false-negative fraction} \times \text{prevalence of AC in study population}}{\text{false-negative fraction} \times \text{prevalence of AC in study population} + \text{specificity} \times \text{prevalence of no AC in study population}}$$

The probabilities of AC being present when the test result is either positive (abnormal) or negative (normal) are shown in Figures 3 to 5. The difference in posttest probability between the positive and negative test results is here called the discriminative power of the test. The wider the

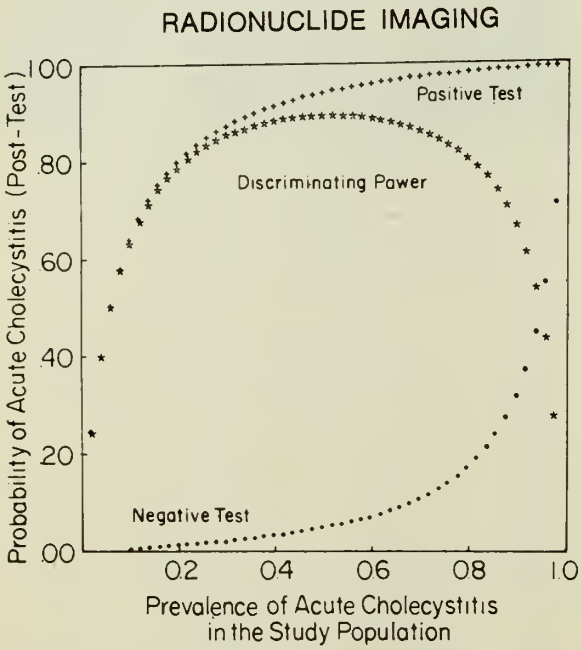

Figure 3.—Radionuclide imaging using technetium Tc 99m IDA. The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis in the study population is shown on the X axis. Note that a wide difference between positive and negative results in a high discriminating power of the test, with a broad curve between the pretest prevalence rate of 20 percent and 80 percent.

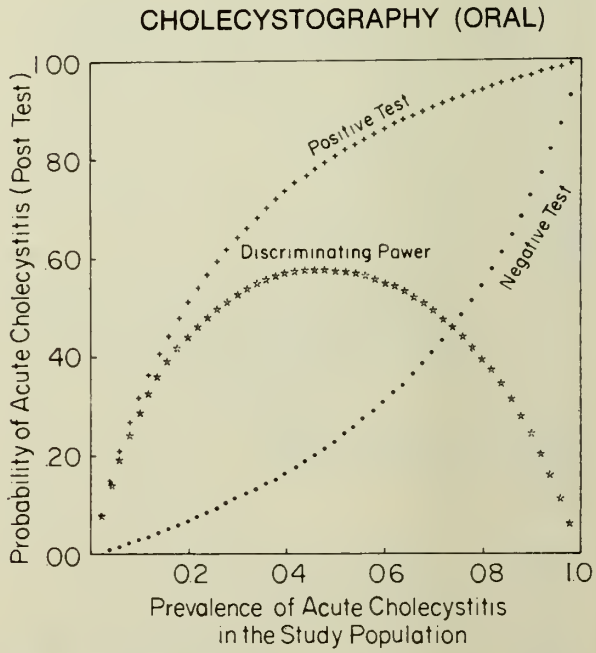

Figure 4.—Cholecystography (oral). The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis (*) in the study population on the X axis. Note that the difference between positive and negative test results is widest at the pretest prevalence rate of 50 percent and the discriminating power of the test decreases above and below this rate.

difference between the positive and negative result, the greater is the discriminating power. A positive finding is considered to confirm and negative finding to exclude AC.

Relative Merits of Gallbladder Imaging Tests

The prevalence of AC in the study population is variable and depends on age, sex, race, parity, nutrition, geography and other factors.[63] Assume that in the Veterans Administration (VA) population, where most subjects are male, the prevalence of AC is 10 percent of all patients with acute right upper quadrant pain and fever of less than three days' duration. The pretesting probability of AC will be 10 percent. After a thorough clinical examination, a primary physician estimates the clinical probability of acute cholecystitis to be greater than 50 percent and orders a cholecystogram, ultrasound and radionuclide imaging studies without knowing the results of any of the tests. A physician does not request these tests first when the probability of AC is felt to be less than 50 percent.

When the finding of the radionuclide imaging test is positive (that is, the gallbladder is not seen),

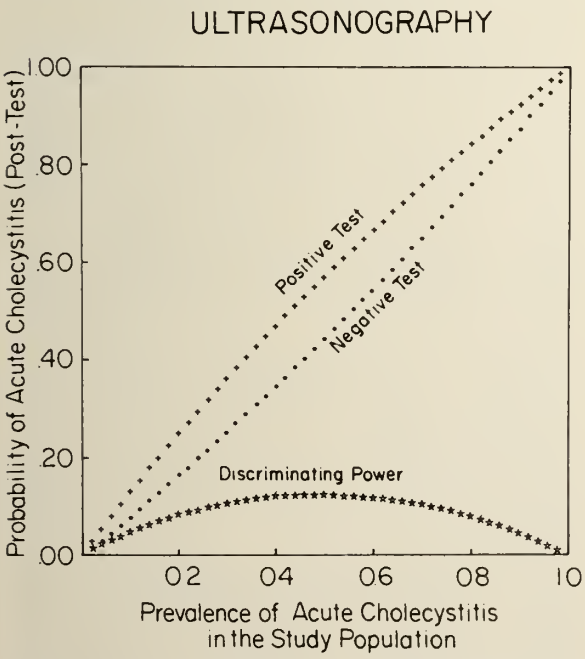

Figure 5.—Ultrasonography. The posttest probability of acute cholecystitis when the test result is either positive (+) or negative (•) is shown on the Y axis and the hypothetical pretest prevalence of acute cholecystitis in the study population (*) on the X axis. Note that both positive and negative result lines run parallel to each other with a narrow separation between them, resulting in a low discriminative power of the test.

the probability of AC increases from 10 percent to 63 percent; and when the test finding is negative (gallbladder seen), the probability decreases from 10 percent to 0.5 percent (Figure 3). Here both positive and negative test results are of value. A positive finding on cholecystography increases the pretest probability from 10 percent to 32 percent and a negative test finding decreases the probability from 10 percent to 3.2 percent (Figure 4), so that both positive and negative test results are of some value. A positive result on an ultrasound study (Figure 5) increases the probability from 10 percent to 12 percent and a negative test finding decreases the probability from 10 percent to 8 percent. So here the positive and negative test results are of little value.

A slightly higher prevalence of AC in the study population may be seen in a county, university or private hospital, where about half of the hospital population are women. Assume that the prevalence of AC in middle-aged obese women with right upper quadrant pain and fever of less than three days' duration is 50 percent. A positive radionuclide imaging study then increases the probability from 50 percent before testing to 95 percent posttesting and a negative test result decreases the probability from 50 percent to 5 percent (Figure 3). Once again both positive and negative test results are of considerable value. A positive finding on a cholecystogram in which a contrast medium is given orally increases the probability from 50 percent to 85 percent and a negative finding decreases the probability from 50 percent to 23 percent (Figure 4). A positive result on ultrasonography, however, increases the probability from 50 percent to 56 percent and a negative result decreases the probability from 50 percent to 45 percent (Figure 5).

A still higher prevalence of 80 percent of AC may be found in an urban or rural health clinic serving mainly American Indians, who have one of the highest recorded incidences of gallbladder disease.[63-66] A positive finding on a radionuclide imaging study increases the probability from 80 percent to 98 percent and a negative finding decreases the probability from 80 percent to 17 percent (Figure 3). A positive result on a cholecystogram increases the probability from 80 percent to 94 percent and a negative result decreases the probability from 80 percent to 57 percent (Figure 4). A positive result on ultrasonography increases the probability from 80 percent to 95 percent and a negative result decreases the prob-

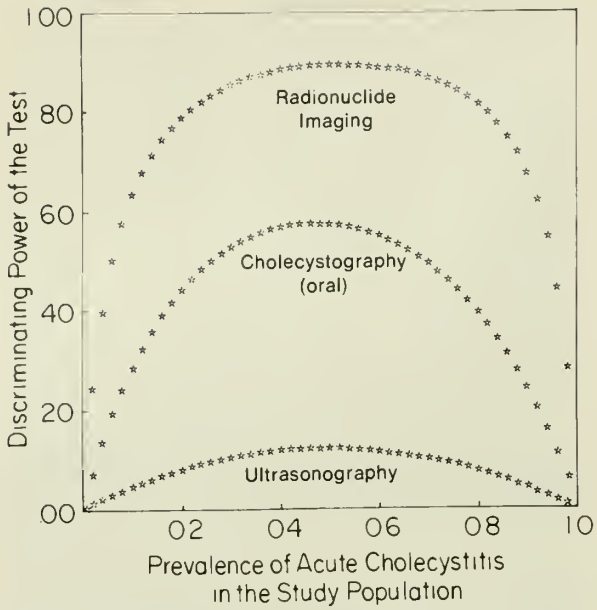

Figure 6.—A comparison of the discriminating power of all three tests in the diagnosis of acute cholecystitis. The hypothetical pretesting prevalence of acute cholecystitis is shown on the X axis. The Y axis shows the power of the test. The value of 1.0 indicates the perfect test.

ability from 80 percent to 75 percent (Figure 5). When the prevalence of AC in the study population exceeds 90 percent, then negative results on any of the tests are not reliable.

The discriminating power of a radionuclide imaging test using technetium Tc 99m is high, with a broad curve for prevalence between 20 percent and 80 percent (Figure 6). Cholecystography (oral) and ultrasonography reach their peak discriminating power at a prevalence rate of 50 percent and have a narrow curve. At a lower prevalence (below 20 percent), radionuclide imaging study shows a rapid rise in discriminating power and superimposes the line for a positive test result. The discriminating line for ultrasonography is almost flat throughout and the line for cholecystography lies between ultrasound study and radionuclide imaging (Figure 6). The discriminating power line descends rapidly downward when the prevalence of AC exceeds 90 percent in the study population.

Comments

As the salient histopathologic feature of AC is cystic duct obstruction,[67] the tests that establish the patency of the cystic duct are most reliable.[68] The exclusion of AC by radionuclide imaging (technetium Tc 99m) can be made in most patients within 30 minutes. Once the diagnosis has been excluded, a physician can then focus attention on an alternative diagnostic workup. Confirmation of the diagnosis of AC, however, requires imaging up to three to four hours. The surgical therapy for AC can thus be instituted within three to four hours after it is first clinically suspected.

About 20 percent of normal gallbladders are not visualized with a single dose of the contrast medium; a double-dose study at 48 hours is required to confirm the diagnosis of AC by cholecystography.[16,17,69] Because almost all patients with AC will have obstruction of the cystic duct and hence nonvisualization of the gallbladder, a cholecystography invariably requires a double dose of the orally given contrast medium. Obviously, this prolongs a hospital stay and delays definitive therapy for as long as two days. An alternative diagnostic workup would also be delayed for 48 hours. In Portland, the average cost of one day in hospital on a general surgical ward is $195. A two-day delay in diagnosis would increase the cost of management of acute cholecystitis by $390 per patient.

In the United States 15 to 20 million people are known to have gallstones. Every year a million new cases are discovered and only half of them are symptomatic, requiring cholecystectomy.[70] Therefore, there is great medical, surgical and socioeconomic risk in equating cholelithiasis with acute cholecystitis. If the total cost of a single cholecystectomy procedure is $3,000, then the annual cost of half a million cholecystectomies in the United States is 1.5 billion dollars. This amount is doubled by simply equating cholelithiasis with acute cholecystitis and treating likewise. Physicians therefore must make a real attempt to distinguish acute cholecystitis from asymptomatic cholelithiasis before submitting a patient to a surgical procedure. The management of AC consists of immediate surgical treatment, whereas chronic cholecystitis is treated by elective surgical procedure.[7]

Before introduction of ultrasonography, symptomatic cholelithiasis was detected by cholecystography. Most of the silent stones were found at autopsy and few by a surgeon while doing an abdominal surgical procedure for some other illness. Many surgeons feel that there is no good reason for treating patients with silent stones. With the ever-increasing frequency of application of abdominal ultrasonography, almost all of silent gallstones can be discovered in vivo.[39] The lesser

discriminatory power of ultrasonography in AC is primarily due to the fact that 50 percent of gallstones are silent and that about 10 percent of cases of AC occur in the absence of cholelithiasis.[71-74] Ultrasonography does not establish the patency of the cystic duct, the salient histopathologic feature of AC.

One recent study used the shape (oval or round) and size (diameter greater than 5 cm) as minor criteria for AC.[75] However, this study did not include normal persons to establish the normal range of shape and size. A normal gallbladder has many shapes to it and may become enlarged after prolonged fasting.[76] Recently another study claimed a high degree of ultrasonographic accuracy (86 percent) in the detection of AC. This level of accuracy was achieved primarily because the authors used local tenderness over the gallbladder region (Murphy's sign) as an ultrasonographic sign for AC.[77] This is a very expensive method of eliciting Murphy's sign, which can be substituted at no additional cost to a patient by careful manual palpation by a physician. Interestingly, the same study showed that the presence of stones did not aid in differentiating acute from chronic cholecystitis. Ideally the parameters used to make a diagnosis by an imaging study should be able to be recorded in an image; otherwise, there would be no need for such a study. Local tenderness obviously cannot be imaged and hence should not be used as evidence of acute cholecystitis. It should be pointed out, however, that ultrasonography is a very important tool in the diagnosis of many abdominal diseases and its role should not be underestimated.[36,37] It is the next logical step once the diagnosis of AC is excluded.

The cost of individual imaging tests that are available for the detection of AC is shown in Table 2. Potentially one could use all of the available diagnostic tests for acute cholecystitis and come up with a bill of $1,099. The analysis used here shows that a physician could reduce the cost by restricting the diagnostic workup to include a plain x-ray film of the abdomen and a radionuclide imaging study and thus reduce the cost from $1,099 to $299 (Table 4). A plain x-ray film of the abdomen is retained because of its other useful intra-abdominal information in general.[12]

Many physicians feel that more tests are ordered than are really required for proper clinical management.[78-81] Years ago it was all right to order cholecystography or cholangiography to diagnose AC. Now with recent advances in hepatobiliary imaging, the question has to be asked whether cholecystography, cholangiography and ultrasonography are really needed in 1982 and beyond to confirm a diagnosis of AC. A decision has to be made here whether or not the number of tests required to confirm AC can be reduced. A delay in this decision will result in multiplication of tests[82-84] and increase in cost of medical care. Recent results have shown that a patient with no contraindication for operation and a positive finding on radionuclide imaging test can be subjected to cholecystectomy for AC without any need for additional testing.[85]

Caution should be exercised in doing an imaging test using technetium Tc 99m IDA. As has been shown in normal subjects,[86] preemptying of the gallbladder with cholecystokinin or a fatty meal is probably an undesirable patient preparation that may result in a high false-positive rate, especially in patients with alcoholism or on total parenteral nutrition.[87] Bayesian analysis is more valid, for instance, when the test carries a constant degree of high precision (sensitivity). The hazards of application of bayesian analysis to tests that show variable sensitivity have been elegantly described in a recent report[88] and should be kept in mind by all clinicians.

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Urology/Sexuality Clinic: Results of Counseling of 67 Men

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Of 67 psychogenically impotent men encountered in a new Urology/Sexuality Clinic during its first 36 months of operation at the University of California Medical Center in San Francisco, 52 returned for more than one urologic counseling visit, rendered individually by the senior author in all cases.

There was a 79 percent success rate in the form of reinstatement of sexual activity, generally within three sessions, at weekly intervals. Success appeared, for the most part, unrelated to age, to previous treatment elsewhere, or even to major medical or surgical problems among some of these men who ranged in age from 18 to 78 years.

A UROLOGY/SEXUALITY CLINIC was founded at the University of California School of Medicine, San Francisco (UCSF), in 1978[1] to make counseling of psychogenic sexual impotency available to clinic patients, using techniques devised by the senior author in 25 years of private practice.[2] The cases of 67 men were evaluated at this clinic during its first 36 months. The records of 52 patients were reviewed in the compilation of results. Although relatively few patients were seen in the first year, there was a progressive increase of referrals during the second and third years, as the clinic became better known.

Patients and Methods

The 67 patients were seen in sequence by the senior author. Their ages ranged between 18 and 82 years, most being 40 to 60 years of age (Table 1). A minimum of two visits was required for inclusion in this study. Of the 67 men interviewed 15 were excluded because only one visit took place or because the patient did not return. At least 20 percent of appointments were broken, sometimes more than once.

Sources of referral were local or distant medical clinics, gynecologic facilities (where a wife had presented the problem of her husband's impotency), and orthopedic, neurologic and psychologic units. Many men had undergone psychotherapy elsewhere or at this medical center, either as an individual patient or as a member of a group (for example, at the Human Sexuality Clinic, UCSF). Many also had received medical treatment from their physicians, primarily hormonal. In a few instances, the original therapist had told the man that the impotency was irreversible.

A definition of sexual potency is obligatory when presenting objective data as to diagnosis and results of therapy of male sexual dysfunction. In previous publications, we cited "psychologic interest, penile erection, intromission and climax (not necessarily ejaculation) . . ." as our measure-

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TABLE 1.—*Status of 52 Patients in First 36 Months of Urology/Sexuality Clinic*

Success		Failure		Excluded	
Number	Percent	Number	Percent	Number	Percent
41	79	11	21	15	21

ments of sexual potency.[3] To compare preoperative and postoperative sexual status in our previous surgical studies, the qualification was added that intercourse was to have occurred at least once during the year preceding and once in the year following the operation. This definition is applicable to this new presentation.

During the first interview (about an hour and a half long), medical history is elicited and physical examination carried out, including careful attention to the genitalia and prostate.[4-6] Urinalysis is done routinely, including microscopic examination of the centrifuged sediment. In addition, after rectal palpation of the prostate gland, a sample of expressed prostatic secretion is collected and examined microscopically.

Therapy actually begins at this first visit, in the form of prolonged, attentive listening. Inquiries about past sexual experience, episodes of partial or complete sexual failure and circumstances relating to the impotency are made thoroughly but in a casual, nonjudgmental manner. The interviewer inquires whether penile erection has recently occurred in the morning, in response to erotic self-play (usually preparation for masturbation), spontaneously, when thinking of a given woman, in response to reading pornographic material or when watching a pornographic movie. A positive reply is evidence of an intact *neurovascular* mechanism.

Since reinstatement of sexual function (whether

TABLE 2.—*Relationship of Age, Number of Visits and Sexual Preference of 52 Men to Results of Urological Counseling*

Age Range	Total Number of Patients	Success of Total Number	Average Number of Visits		Sexual Preference	
			Success	Failure	Het.*	Hom.†
18-29	7	6	2.5	3.0	7	0
30-39	6	4	2.3	2.1	5	1(S)
40-49	9	7	3.4	2.0	6	3(2S) (1D)‡
50-59	16	11	2.5	2.1	16	0
60-69	8	7	2.6	2.0	8	0
70-79	6	6	2.4	0.0	6	0
TOTAL	52	41			48	4

(S) = single, (D) = divorced.

*Heterosexual.
†Homosexual.
‡This man was originally heterosexual. He had married and sired 3 children. Homosexual activity occurred during marriage and exclusively after divorce.

TABLE 3.—*Relationship of Age, Duration of Impotence, Major Organic/Surgical History and Marital Status*

Age Range	Total Number of Patients	Average Duration of Impotence		Previous Organic or Surgical Problems		Marital Status			
		Success	Failure	Success	Failure	S	M	D	W
18-29	7(6/1)*	3 yrs	3 mos	yes—2 no—4	no—1(S)	6	1	0	0
30-39	6(4/2)	4 yrs	4.5 yrs	yes—0 no—4	yes—1(M) no—1(S)	4	2	0	0
40-49	9(6/3)	10 yrs	17 yrs	yes—2 no—4	yes—1(S) no—2(M;D)	4	3	2	0
50-59	16(11/5)	4 yrs	4 yrs	yes—6 no—5	yes—4(3D;1M) no—1(M)	1	7	8	0
60-69	8(7/1)	7 yrs	3 yrs	yes—3 no—4	yes—0 no—1(M)	1	6	1	0
70-79	6(6/0)	3 yrs	0	yes—1 no—5	yes—0 no—0	0	2	0	4

(S) = single, (M) = married, (D) = divorced, (W) = widowed.

*The numerator refers to success and the denominator to failure in each age range.

erectile or ejaculatory competency) must involve a *willing, available partner,* the interviewer asks whether such a partner exists. Because situational impotency is common, involving a *specific time, place* and *partner,* it is imperative to direct therapy sessions toward coitus with this actual or potential person. Recovery of sexual potency *in absentia* (erection but no partner) is theoretically constructive but lies outside the limits of our definition. Time spent with the patient by a physician who is secure in his own sexuality becomes therapeutic per se. Taking a hurried history or making a cursory physical examination is to be avoided. Most patients sense possible indifference and haste in an examiner, and may perceive the counselor as ill at ease with sexual problems.

In most instances the period of follow-up was six months or longer. It was not part of our protocol to keep records about possible relapses beyond six months because we considered this as an intrusion upon privacy. When patients did not return to the clinic or did not contact us after six months from the time of the original visit, we assumed that they were progressing satisfactorily, on the premise that their original motivation for help had been substantial and since we consistently invited them to see us again if necessary. (Of course, any recurrent impotency could well dissuade the patients from a second try with our methods.) Several patients were contacted at random by telephone during preparation of this report. They all stated that the success (or failure) of therapy had remained unchanged. Yet we are unable to state definitely the duration of reinstated sexual function of the group overall.

Results

Most therapeutic successes for our patients occurred in the age decades 18 to 29 and also 60 to 80 years, whereas most failures in the age decade 50 to 59 years (Table 2). Reinstatement of satisfactory sexual performance occurred in 41 of the 52 patients, a success rate of 79 percent. It is noteworthy that the good results were not limited to younger men—since 6 of our 41 successful results were in men between 70 and 79 years of age.

Most patients were able to engage in satisfactory sexual intercourse after two or three visits to the clinic. There were no major differences between the number of visits recorded for the two groups. For no discernible reason more visits were required to reach success in the 40 to 49 years age group than in any of the others. Among the 11 men who did not respond to counseling were some who had serious organic problems, such as a debilitating illness, or some who had had previous major surgical interventions. Yet medical or surgical factors (such as diabetes or postradical prostatectomy status) did not invariably perpetuate impotency (Table 2). There were no major differences between the number of visits in the success or failure groups.

Most men in our older successful groups were married (Table 3), although most widowers were within the oldest group. In general, duration of impotency, previous organic or surgical problems and marital status were not critical influences on outcome of urologic counseling. However, availability of a willing partner was important but not essential for reinstatement of sexual potency in response to urologic counseling.

The therapeutic successes or failures of the treatment of both homosexual and heterosexual patients were combined in our aggregation of data. Our experience with men of homosexual preference was limited. Of those we encountered, primarily in the second and third years in the existence of our clinic, there seemed to be as favorable a chance for reinstatement of sexual potency as among heterosexual men.

The patients' educational and marital status varied widely.

Comment

In general, data derived from the present study corroborate the results of our previous publications, which indicated that despite organic disease, sequelae of serious surgical or traumatic problems and previously unsuccessful therapy, psychogenic sexual impotency can often be successfully overcome by means of urologic counseling.[1-6]

Selection of patients to receive urologic counseling evolved primarily with the clinical acuity of a referring colleague or the urologic counselor, or both. Motivation for regaining potency was often less in this clinic situation than in private practice.

Various methods and tests for classification and treatment of men with sexual dysfunction are being reported with ever-increasing frequency.[7] This growing interest in analysis of impotency is important and all investigations that will result in better diagnosis and treatment of this problem should be encouraged.

Quite recently, Spark and his colleagues sought

to cast doubt upon psychogenic causes as a major category of male impotency.[8] They properly suggested that at least minimal hormonal evaluation be done in a study of impotent men. Their own series of patients bore an abnormally high incidence of severe endocrine and malignant causes, thereby showing other bases for impotency but not refuting the major position of psychogenic causes.[9]

Increasing interest is developing in surgical installation of inflatable[10] or semirigid[11] penile prosthetic devices to simulate physiologic penile erection. Scott and his colleagues have emphasized the need for thorough psychiatric evaluation of prospective candidates for such surgical procedures.[10] Quite recently, Gerstenberger, Osborne and Furlow published their experiences with inflatable penile prostheses, identifying their preoperative psychologic studies.[12] This group has begun to use penile prostheses in some psychogenically impotent men and are aggregating their promising results with these patients.

The therapeutic approach in our clinic consists essentially of *attentive listening and moral support* and concurrently dealing with the *physical component* of impotency, such as congestive prostatitis, when appropriate. In addition, during the first interview we identify and specify an *emotional component,* namely subconscious fear of performance failure. In general, a favorable outcome ensues within three sessions at weekly intervals. The availability of a partner at the time of therapy is per se a favorable factor. Nevertheless, it was not always correlated with the successful outcome of counseling—and vice versa.

In the above-described clinical analysis of psychogenic impotency, the initial and continuing diagnostic and therapeutic approaches made no provision for objective identification of wholly organic causes. Thus nocturnal penile tumescence studies[13] and tests of penile temperature,[14] to specify but a few,[15-17] were not done.

We object to casual administration of hormonal therapy in that its effect, if any, really represents a three-way interaction between an ostensibly knowledgeable physician, an expectant patient and a purportedly useful medication. Encouragement toward reinstatement of potency appears to us the most vital and useful technique according to our experience.

Urologic counseling is straightforward, noninvasive and generally of brief duration. Applying this approach on behalf of a psychogenically impotent man does not preclude subsequent psychoanalytic or surgical measures, if necessary. Therefore, we recommend, based upon experience and our acceptably good results, that methods such as elucidated in this report be applied as a primary modality. We readily acknowledge that ours is neither the only nor the most complete technique. As pragmatists who seek physical reinstatement of sexual function, we believe that therapeutic progress from innocuous to more complex measures constitutes a rational program.

Obviously, hormonal bases alone cannot explain the totality and complexity of factors fundamental to the human sex drive.[18]

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The Differential Diagnosis of Pleural Effusions

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The presence of pleural effusion enables a physician to obtain a specimen of a body cavity fluid easily. With a systematic analysis of the pleural fluid, in conjunction with the clinical features and ancillary laboratory data, a clinician should be able to arrive at either a presumptive or definitive diagnosis in approximately 90 percent of cases. Selectivity should be exercised in ordering analyses on pleural fluid. The first important deductive step is to decide whether the effusion is a transudate (due to imbalances in hydrostatic or oncotic pressures) or an exudate (inflammatory); serum protein and lactate dehydrogenase measurements will be decisive. The differential diagnosis of a transudate is relatively limited and usually easily discernible from the clinical presentation. The differential diagnosis of exudate poses a more difficult challenge for clinicians. The use of certain pleural fluid tests such as leukocyte count and differential, glucose, pH and, when indicated, pleural fluid amylase determinations, helps to narrow the differential diagnosis of an exudative pleural effusion.

CLINICIANS FREQUENTLY are confronted with patients with pleural effusions. The presence of this pleural fluid provides the simple opportunity to get a specimen of a body cavity fluid to support the clinical impression. Knowledge of the physiology of pleural fluid formation and analysis of the cellular content and chemistry of these effusions, in conjunction with the history, physical examination and ancillary laboratory data, should enable a clinician to reach a presumptive or definitive diagnosis in about 90 percent of patients with pleural effusions. Pleural fluid analysis is similar to other laboratory tests in medicine; these tests rarely provide a definitive diagnosis but support the clinical impression. The only pleural fluid findings that provide a definitive diagnosis are (1) the presence of malignant cells, (2) a positive Gram stain, acid-fast bacilli (AFB) stain or pleural fluid culture and (3) the presence of lupus erythematosus (LE) cells.

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Physiology of Pleural Fluid Formation

The passage of pleural fluid across the pleural membrane in normal humans is dependent on the opposing hydrostatic and oncotic pressures acting on both the visceral and parietal pleural membranes.[1,2] Normally, the oncotic pressures on both

ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
LDH = lactate dehydrogenase
LE = lupus erythematosus
Pa_{O_2} = arterial oxygen partial pressure (tension)

sides of the parietal and visceral pleura are equal; thus, the difference in forces is attributable to the inequality in hydrostatic pressures between the systemic circulation that supplies the parietal pleura and the lower pressure pulmonary circulation that supplies the visceral pleura. The magnitude of these forces suggests that fluid is formed at the parietal pleural surface and absorbed by the visceral pleural capillaries in a dynamic state. Protein and red blood cells, however, are absorbed only by the lymphatic vessels draining the pleural space.[3] Despite these forces, a thin layer of liquid remains in the pleural space in the normal state; this alkaline fluid contains less than 2 grams per dl of protein and a low number of mononuclear cells.[4,5]

Conditions Under Which Abnormal Amounts of Pleural Fluid Develop

Abnormal amounts of pleural fluid accumulate when there is an increase in hydrostatic pressure (congestive heart failure), a decrease in colloid osmotic pressure (severe hypoalbuminemia), an increase in capillary permeability (pneumonia), increased intrapleural negative pressure (atelectasis) and decreased lymphatic drainage (mediastinal carcinomatosis). Blood may enter the pleural space because of trauma (blunt injury, thoracentesis, tumor erosion of a vessel), and chyle may accumulate from rupture of the thoracic duct and disruption of the mediastinal parietal pleura.

Clinical Features of Pleural Effusions

The symptoms that cause a patient to seek medical attention usually are not due to the presence of the effusion itself but to the underlying disease process. However, a large effusion may cause dyspnea at rest in patients with underlying lung disease or dyspnea on exertion in patients with normal lungs.

When a pleural effusion develops the lung is separated from the chest wall by a layer of fluid that interferes with sound transmission. The physical findings with a pleural effusion will vary depending on the size of the effusion, involvement of the underlying lung and the degree of lung compression. Physical findings with varying degrees of pleural fluid are summarized in Table 1.

There are important points to remember about physical findings with a pleural effusion:

- Physical findings may be normal when there is less than 300 ml of fluid in the pleural space.
- It generally takes more than 1,000 ml of pleural fluid to cause a contralateral mediastinal shift.
- When a contralateral mediastinal shift does not occur with the critical or apparent critical volume of fluid, the following four diagnoses should be considered: (1) carcinoma of the mainstem bronchus with atelectasis of the ipsilateral lung, (2) a fixed mediastinum due to neoplastic lymph nodes, (3) malignant mesothelioma and (4) pronounced infiltration of the ipsilateral lung, usually with tumor.

Appearance of Pleural Fluid on Chest Roentgenogram

Free pleural fluid has a characteristic appearance on an upright chest roentgenogram in the absence of pleural disease. It produces a homogeneous density through which lung markings may be discerned. The upper margin of the fluid forms a meniscus (concave upward) at the lateral chest wall. Small effusions may reveal only blunting of the costophrenic angle or may be seen as a "thickening" of either the minor fissure on the posteroanterior view or the minor and major fissures on the lateral view. A critical amount of fluid (probably 200 ml) needs to be present in an adult to be detectable on an upright chest roentgenogram. A lateral decubitus view, however, will show lesser amounts of free fluid. Occasionally fluid will be situated between the bottom of the lung and the diaphragm (subpulmonic effusion). Subpulmonic effusion can be confirmed with a lateral decubitus view. Fluid may loculate in the pleural space, including the intralobar fissures, and may produce a "pseudotumor."

Indications for Thoracentesis

Diagnostic

When a pleural effusion is recognized, a diagnostic thoracentesis should be done either to support the clinical impression or for further diagnostic information when the clinical situation is unclear. Exceptions to this rule might be when the clinical diagnosis is secure and only a small amount of pleural fluid is present—that is, when

TABLE 1.—*Physical Signs of Pleural Effusion*

Amount of Effusion	*Expansion*	*Fremitus*	*Percussion*	*Breath Sounds*	*Contralateral Mediastinal Shift*
1. Small effusion ..	N	N	N	v	0
2. 300-1,000 ml ...	↓	↓	f	↓v	0
3. 1,000-2,000 ml ..	↓↓	↓	f	↓↓bv	+
4. >2,000 ml	↓↓↓	↓↓	f	↓↓↓−0	++

N = normal; ↓ = decrease; f = flat; v = vesicular; bv = bronchovesicular; 0 = absent; + = present.

the benefit-to-risk ratio is small—or in a patient with uncomplicated congestive heart failure (afebrile, a compatible clinical history and arterial oxygen tension (Pa_{O_2}) not out of proportion to the clinical situation). In the above situations, continued observation without thoracentesis may be warranted. However, a clinician should not hesitate to do a thoracentesis if the situation changes.

Therapeutic

When a patient with a large effusion, usually due to malignancy, is dyspneic because of the effusion, a therapeutic thoracentesis should be carried out. The dyspnea in these instances probably is related more to neurogenic factors in compressed lung tissue than to oxygen chemosensors, as most patients have a relief of dyspnea following thoracentesis even if the Pa_{O_2} falls.[6,7] Not more than 1,000 ml of pleural fluid should be removed at one sitting without monitoring pleural fluid pressure.[8]

Complications of Thoracentesis

Complications of thoracentesis include pneumothorax, hemorrhage (hematoma, intrapleural,[9] intra-abdominal[10]), empyema, pain, hypoxemia, liver or spleen[11] puncture and unilateral pulmonary edema.[12] Pneumothorax can be avoided by inserting the needle one interspace below the level where the physical findings change. One should do the thoracentesis at the highest interspace dictated by physical examination; this will avoid spleen or liver puncture. Oxygen by nasal cannula should be administered during and for 24 hours after a therapeutic thoracentesis to prevent the fall of Pa_{O_2} that commonly occurs.[6,7]

Pleural Fluid Analysis

When the thoracentesis is done, the fluid should be analyzed in a systematic manner. Color, odor and character of the fluid should be noted. The following laboratory tests are commonly carried out on pleural fluid: leukocyte count and differential, erythrocyte count, total protein, glucose, lactate dehydrogenase (LDH), amylase and pH determinations; Wright, Gram and AFB stains; aerobic, anaerobic, tuberculosis and fungal cultures; and cytology. *All* of these tests do not need to be done on all fluids. The expense is exorbitant and the diagnostic usefulness of the entire battery is small. A clinician should select the appropriate tests depending on the clinical situation. For example, a pleural fluid amylase level should be ordered only when pancreatitis, pancreatic pseudocyst or esophageal rupture is suspected.

Observation

All transudative fluids and some exudates are clear and straw colored. Other hints from observation include a milky color that suggests chylothorax, a reddish tinge indicating blood and an anchovy color that occurs when an amebic liver abscess has ruptured into the pleural space. Both a large number of leukocytes and increased lipids will make the pleural fluid appear turbid. A simple bedside test for differentiating elevated leukocyte counts from lipids is to centrifuge the fluid; if the supernatant clears, the turbidity is due to leukocytes. With chylothorax, chylomicrons produce a whitish layer on top of the centrifuged fluid. Pus aspirated from the pleural space establishes a diagnosis of empyema. Anaerobic empyemas have a characteristic putrid color in 50 percent to 60 percent of cases. A very viscous fluid that is hemorrhagic suggests a malignant mesothelioma.

Leukocytes

If the leukocyte count is more than 1,000 per μl, the fluid is likely an exudate. Conversely, leukocyte counts less than 1,000 per μl suggest that a fluid is a transudate.[13] Neutrophils predominate early in inflammatory effusions due to pneumonia, pulmonary infarction, pancreatitis, tuberculosis or lupus. Several days after the acute

insult to the pleura, mononuclear cells predominate in the effusion. Pleural macrophages appear early and are followed by lymphocytes.[14] Mononuclear cells predominate in transudative pleural effusions and chronic exudative effusions[15] (caused by, for example, tuberculosis, lymphoma, carcinoma, uremic pleurisy or rheumatoid pleurisy). The reason that these exudative effusions are mononuclear predominant is that patients with these diseases usually are not seen in the acute phase; by the time a thoracentesis is done the acute inflammatory process has subsided and the polymorphonuclear leukocyte predominance has changed to a mononuclear predominance.

Finding pleural fluid eosinophilia (more than 10 percent of total leukocytes) does not provide a specific diagnosis but offers certain useful information. These effusions are exudates with a large population of lymphocytes and tend to be self-limiting and with a favorable outcome.[16] The presence of the eosinophils makes the diagnosis of tuberculosis unlikely.[13,17] Eosinophils frequently are found when blood or air has entered the pleural space and thus may be noted with a pneumothorax or hemothorax. Pleural fluid eosinophilia also may be found with pulmonary infarction, polyarteritis nodosa and parasitic and fungal disease.[17]

Erythrocytes

The presence of 5,000 to 10,000 erythrocytes per μl will cause fluid to appear hemorrhagic. When pleural fluid is grossly hemorrhagic in the absence of trauma, malignancy must be considered. When the erythrocyte count is more than 100,000 per μl, the diagnosis is usually a malignant lesion or trauma or, less likely, pulmonary infarction.[13,18] Transudative effusions are rarely sanguineous and the finding of a bloody effusion in the setting of congestive heart failure should raise the possibility of a concomitant pulmonary infarction, though 10 percent of pleural effusions due to congestive heart failure alone may be serosanguineous.[19] Tuberculous pleural effusions are usually serous or serosanguineous (less than 10 percent) and rarely grossly bloody. There are two bedside tests that can be used to determine whether the thoracentesis is traumatic or the fluid is actually bloody: (1) Measure the hematocrit of the fluid and compare it with the blood hematocrit. Identical hematocrit ranges usually indicate traumatic thoracentesis, but this finding can be seen with chest trauma and, rarely, malignancy. (2) Note whether the pleural fluid clots. A traumatic thoracentesis fluid should clot within several minutes, whereas pleural fluid that has been present for several hours to days will become defibrinated and will not form a good clot.

Glucose

A normal pleural fluid glucose value (more than 60 mg per dl, or a pleural fluid-to-serum ratio of over 0.5) is not particularly helpful; however, a low pleural fluid glucose level (less than 60 mg per dl or a pleural fluid-to-serum ratio of under 0.5) will help narrow the differential diagnosis of the exudative pleural effusion. The following diagnoses have been associated with a low pleural fluid glucose level: (1) rheumatoid pleurisy—usually less than 30 mg per dl[20]; (2) empyema—glucose level almost always low and ranges between 0 and 60 mg per dl[21,22]; (3) carcinoma—glucose concentration decreased in approximately a third of patients, especially those with chronic effusions, usually between 20 and 60 mg per dl[23,24]; (4) tuberculosis—probably less than 20 percent of cases in which the level is usually between 30 and 60 mg per dl; (5) esophageal rupture—glucose almost always low due to anaerobic empyema[25]; (6) lupus pleuritis—incidence not known, but decreased glucose concentration is usually transient.[26]

The mechanisms responsible for a low pleural fluid glucose level appear to be a combination of enhanced glycolysis by either pleural fluid cells, bacteria or pleural tissue in conjunction with an impairment to transport of glucose from blood to pleural fluid.[22,24,27,28] For the most accurate interpretation of pleural fluid glucose level, thoracentesis should be carried out while a patient is in a fasting state and a serum glucose determination obtained at the same time. When pleural fluid is collected for glucose analysis, fluid must either be frozen or stored with a substance such as sodium fluoride that prevents in vitro glycolysis.

Total Protein and LDH, Transudates vs Exudates

In determining the differential diagnosis of a pleural effusion, it is important to classify the fluid as either a transudate or an exudate. The differential diagnosis of transudate is limited and the clinical diagnosis usually is apparent from the history and physical examination. Exudative pleural effusions have many more diagnostic possibilities and occur most commonly when there is an inflammatory process involving the pleura. When

inflammation affects the pleura, proteins leak from the pleural capillaries into the pleural space; thus, it would be expected that total protein and LDH levels would increase. If any one of the three following criteria is present, the fluid is usually an exudate: (1) a pleural fluid to serum protein ratio of over 0.5, (2) a pleural fluid LDH level of more than 200 IU and (3) a pleural fluid-to-serum LDH ratio of over 0.6.[29] The various sources of transudates and exudates are shown in Table 2.

Amylase

An elevated pleural fluid amylase value (over 160 Somogyi units per dl), or at least twice the serum amylase value suggests one of the four following diagnoses: acute pancreatitis[30,31]; pancreatic pseudocyst[30,31]; esophageal rupture,[32] and, rarely, primary or metastatic carcinoma of the lung.[33] An increased concentration of pleural fluid amylase (500-2,000 Somogyi units per dl) probably results from lymphatic passage or seepage of the enzyme across the diaphragm or by direct transdiaphragmatic communication (in the case of more than 20,000 Somogyi units per dl) between the pleural space and abdominal cavity. An additional hypothesis is that leakage of the enzyme from blood to pleural space reflects impaired reabsorption due to a damaged pleural surface.

TABLE 2.—*Causes of Pleural Effusions*

Transudates
- Congestive heart failure
- Cirrhosis with ascites
- Nephrotic syndrome
- Hypoalbuminemia
- Peritoneal dialysis
- Atelectasis, acute
- Superior vena cava obstruction
- Subclavian catheter misplacement
- Early mediastinal malignancy

Exudates
- Parapneumonic effusion (bacterial pneumonia)
- Pulmonary infarction
- Malignancy (direct pleural involvement, late mediastinal involvement)
- Viral disease
- Connective tissue disease (lupus, rheumatoid, mixed)
- Tuberculosis
- Fungal disease
- Parasitic disease *(Entamoeba histolytica, Paragonimus westermani)*
- Gastrointestinal disease (pancreatitis, esophageal rupture, subphrenic abscess)
- Drug reaction (nitrofurantoin, methysergide)
- Asbestos
- Meigs' syndrome
- Postmyocardial infarction and postcardiac surgical operation
- Trapped lung
- Lymphatic abnormality
- Uremic pleurisy
- Atelectasis, chronic
- Chylothorax
- Sarcoidosis

Lipids

Chylous effusions (chylothorax) occur when the contents of the thoracic duct empty into the pleural space. The most common cause is malignancy, usually lymphoma, which causes a rupture of the thoracic duct, drainage into the mediastinum and then extension into the pleural space.[34] Other causes of a chylothorax are surgical procedures and trauma. These chylous effusions contain chylomicrons and a high level of triglycerides.[35] If a thoracentesis is done within a few hours of a meal, chylomicrons can be seen as the top whitish layer in a centrifuged specimen. In general, triglyceride levels will be more than twice the concentration of that in a simultaneous serum specimen. These fluids also will stain positive with Sudan III.

Chyliform effusions are long-standing effusions seen in tuberculous pleurisy, trapped lung* or rheumatoid pleurisy and are characterized by high concentrations of cholesterol, low levels of triglycerides and no chylomicrons; they do not stain positive with Sudan III.[36] The high concentration of cholesterol is due to cellular degeneration.

pH

The finding of a low pleural fluid pH (less than 7.30) provides a clinician with the following information: (1) The fluid is always an exudate; (2) the differential diagnosis of the exudate is narrowed to empyema, malignancy, rheumatoid pleurisy, lupus pleuritis, tuberculosis and esophageal rupture[37]; (3) a parapneumonic effusion is either an empyema or will behave clinically like an empyema and usually requires chest tube drainage,[38] and (4) the finding has diagnostic, prognostic and therapeutic implications in malignant effusions.[39] Pleural fluid pH should be obtained as an arterial blood gas in a heparinized syringe and maintained anaerobically on ice until analyzed.

Cytology

About 25 to 50 ml of pleural fluid is all that is required for adequate cytologic examination. A small amount of heparin should be added to the

*A trapped lung results from infection in the pleural space when a fibrous "peel" encases the lung and does not permit expansion to the chest wall.

specimen to inhibit clotting, which could cause cellular distortion. The specimen should be brought to the laboratory immediately for processing; if this is impossible, the fluid should be kept refrigerated until it can be taken to the laboratory. In cases of proved carcinoma of the pleura, cytology is positive in approximately 50 percent to 70 percent of patients.[40-42] Some of the false-negative cytology findings may be due to improper handling of specimens, a long-standing effusion with many degenerative cells or a lack of interest or expertise in the pathology laboratory. Pleural effusions associated with malignancy may not be due to carcinomatous involvement of the pleura but to lymphatic obstruction, endobronchial obstruction with pneumonia or endobronchial obstruction with atelectasis. Characteristics that suggest malignancy include cells that have large nuclei, a high nucleocytoplasmic ratio and clumping. If the first pleural fluid specimen is negative and carcinoma is suspected, another specimen of fluid should be obtained that would yield fresher cells and a lower percentage of degenerative mesothelial cells. The yield of repeat cytology in carcinoma of the pleura is 17 percent to 22 percent.[42,43]

Staining of Pleural Fluid

A Wright's stain of centrifuged pleural fluid will enable better differentiation of neutrophils from mononuclear cells, will aid in the identification of cosinophils and will enable the identification of LE cells pathognomonic of lupus pleuritis. Differentiation of the types of mononuclear cells is not reliable with Wright's stain and requires special staining techniques. A Gram stain of centrifuged pleural fluid should be obtained routinely in an attempt to establish the diagnosis of pleural space infection. Smears of pleural fluid for AFB are positive in approximately 20 percent to 30 percent of patients with tuberculous pleurisy.[44]

Indication for Pleural Biopsy

A pleural biopsy with a Cope's or Abrams' needle should be done where there is an undiagnosed exudative pleural effusion. Usually it is diagnostic only when there is a mononuclear-predominant exudate such as found in tuberculosis, carcinoma and lymphoma. Carcinoma may be diagnosed on pleural biopsy in approximately 60 percent of cases of carcinoma of the pleura.[42] The yield probably can be increased if the operator takes three to five biopsy specimens from two separate sites. Closed pleural biopsy in tuberculous pleurisy will be positive in 70 percent to 85 percent of patients either by tissue histology or culture of the tissue specimens.[45]

Common Causes of Pleural Effusions

Congestive Heart Failure

Pleural effusions (see Table 3) occur in congestive heart failure when there is combined right- and left-sided heart failure, that is, both systemic and pulmonary venous hypertension. Thus, a patient will have distended neck veins, positive hepatojugular reflux, edema, rales and a left ventricular gallop. The effusions of congestive heart failure usually are bilateral but can be unilateral and have been found to occur in the left side only in up to 20 percent of cases.[46,47] This transudative effusion is clear and straw colored and generally contains less than 1,000 cells per μl. The cells are predominantly lymphocytes and mesothelial cells.[48] The protein concentration is usually less than 3 grams per dl but occasionally will increase to higher levels or have a pleural fluid-to-serum ratio of over 0.5 in chronic congestive heart failure treated with diuretics.[49]

Cirrhosis of the Liver

Pleural effusions will develop in approximately 5 percent of patients with cirrhosis and clinically demonstrable ascites.[50] The effusions are usually right sided but may be bilateral or isolated to the left side. The fluid probably moves from the peritoneal to pleural cavity via defects in the diaphragm or via diaphragmatic lymphatic channels. The fluid is a transudate with cell counts generally less than 500 per μl, with the cells predominantly mononuclear. The characteristics of the pleural and peritoneal fluid are similar, though the pleural fluid has a slightly higher protein concentration.

Parapneumonic Effusions and Empyemas

A parapneumonic effusion is any pleural effusion associated with a bacterial pneumonia or lung abscess. The fluid may be clear or turbid and sterile and resolve without sequelae (uncomplicated parapneumonic) with antibiotic treatment directed at the pneumonia. Or the fluid may be frankly purulent and loculate in the pleural space (empyema or complicated parapneumonic). Parapneumonic effusions commonly occur following bacterial pneumonias. They have been found in

TABLE 3.—*Pleural Fluid Characteristics in Common Diseases**

Diagnosis	*Appearance*	*Total Leukocytes (per µl)*	*Predominant Leukocytes*	*RBC (per µl)*	*Protein*	*Glucose*	*LDH*	*Amylase*	*pH*	*Comment*
Transudates										
Congestive heart failure	Clear, straw-colored	<1,000	M	0-1,000	PF/S<0.5	PF=S	PF/S<0.6 <200 IU/L	≤S	>7.40	Usually presence of biventricular failure
Cirrhosis	Clear, straw-colored	<500	M	<1,000	PF/S<0.5	PF=S	PF/S<0.6 <200 IU/L	≤S	>7.40	Incidence 5% of cirrhotic patients with ascites
Exudates										
Parapneumonic (uncomplicated)	Turbid	5,000-25,000	P	<5,000	PF/S>0.5	PF=S	PF/S>0.6	≤S	>7.30	Resolves with antibiotics only
Empyema	Turbid to purulent	25,000-100,000	P	<5,000	PF/S>0.5	0-60 mg/dl PF/S<0.5	PF/S>0.6 some >1,000 IU/L	≤S	<7.30	Requires tube drainage
Pulmonary infarction	Straw-colored to bloody	5,000-15,000	P	1,000-100,000	PF/S>0.5	PF=S	PF/S>0.6	≤S	>7.30	Small effusion with basal alveolar infiltrate and elevated diaphragm
Tuberculosis	Straw-colored to serosanguineous	5,000-10,000	M	<10,000	PF/S>0.5	PF=S or <60 mg/dl	PF/S>0.6	≤S	<or>7.30	Positive PPD, AFB stain and culture of pleural tissue often diagnostic
Rheumatoid disease	Turbid, green to yellow	1,000-20,000	M or P	<1,000	PF/S>0.5	<30 mg/dl	Often >1,000 IU/L	≤S	<7.30	Men, rheumatoid nodules, low pleural fluid complement
Carcinoma	Turbid to bloody	<10,000	M	1,000 to several 100,000	PF/S>0.5	PF=S or <60 mg/dl	PF/S>0.6	≤S	<or>7.30	Cytology and pleural biopsy enable diagnosis in 80%
Pancreatitis	Turbid	5,000-20,000	P	1,000-10,00	PF/S>0.5	PF=S	PF/S>0.6	PF/S>2	>7.30	Occurs in 6% of cases of pancreatitis: left sided in 70%

RBC = red blood cells; LDH = lactate dehydrogenase; M = mononuclear; PF = pleural fluid; S = serum; P = polymorphonuclear; PPD = tuberculin skin test with purified protein derivative; AFB = acid-fast bacilli.

*Reproduced with permission from Sahn SA: Pulmonary disease, *In* Reller LB, et al (Eds): Clinical Internal Medicine. Boston, Little, Brown, 1979, pp 106-107

approximately 60 percent of patients after *Streptococcus pneumoniae* pneumonia[51] and in close to 50 percent of patients with all forms of bacterial pneumonia.[52] Pleural effusions with viral pneumonia and *Mycoplasma pneumoniae* pneumonia occur in about 20 percent of patients; these effusions are small and usually can only be seen by a lateral decubitus view on x-ray study.[53] The exact incidence of pleural effusions in Legionnaires' disease is unknown, but it probably falls somewhere between that of viral and bacterial pneumonias.

Uncomplicated parapneumonic effusions are exudates with leukocyte counts ranging generally from 5,000 to 25,000 per μl. They are neutrophil predominant with high protein concentrations, normal glucose levels and a pH of over 7.30. With antibiotic therapy alone, these effusions resolve over a few days without pleural space loculation.[38] Empyema is diagnosed by aspirating purulent fluid from the pleural space. However, certain nonpurulent pleural effusions have either a positive Gram stain, positive culture or a low pleural fluid pH (complicated parapneumonic effusion), behave like an empyema and form loculations in the pleural space.[38] With empyemas there will generally be leukocyte counts of more than 50,000 per μl (though counts can be extremely low), a low pleural fluid glucose level (0 to 60 mg per dl) and a low pleural fluid pH (less than 7.30). The most common organisms responsible for empyemas today are anaerobic organisms, *Staphylococcus aureus* and Gram-negative aerobic bacilli.[54]

Empyema should be suspected in the presence of pneumonia when a patient continues to be febrile despite antibiotic therapy and in whom a pleural effusion or increasing amounts of pleural fluid develop. A diagnostic thoracentesis should be done immediately in the latter two situations and when fluid is observed on radiograph in the first instance.

The treatment of empyema consists of immediate and complete drainage of the pleural space by chest tube and administration of appropriate antimicrobial agents selected on the basis of aerobic and anaerobic cultures. If adequate pleural space drainage cannot be accomplished by chest tube and the patient remains septic, thoracotomy needs to be done to establish effective drainage.

Pulmonary Infarction

Pleural effusions in pulmonary infarction are generally small, serosanguineous exudates that are neutrophil predominant. However, if the thoracentesis is delayed for several days following the acute injury, a mononuclear-predominant effusion may occur. Finding a bloody pleural effusion is one of the most helpful differential points between pulmonary infarction and pneumonia. The combination of diaphragmatic elevation, a basal peripheral pulmonary infiltrate and a small pleural effusion composes a radiographic triad suggestive of pulmonary infarction. In patients with pulmonary emboli without infarction a transudative effusion due to atelectasis may develop.

Carcinomatous Pleurisy

Carcinoma involving the pleura signals incurability. It represents either secondary metastasis from lung cancer or tertiary spread from a primary lesion below the diaphragm.[55] The most common primary tumors metastasizing to the pleura are of the lung, breast, stomach and ovary.[56] Carcinomatous pleurisy is almost always associated with mediastinal lymph node carcinomatosis. Impaired lymphatic drainage due to the infiltrated mediastinal lymph nodes is the primary pathogenic mechanism for accumulation of pleural fluid.[55,56] A malignant pleural effusion is usually moderate to massive in size and is frequently hemorrhagic with low leukocyte counts and a mononuclear predominance.[56] A massive bloody effusion in the absence of trauma is almost always due to malignancy.[13,57] The finding of a low glucose level and low pH in a malignant effusion suggests that the effusion has been present for several months, that the malignancy is far advanced, survival is in weeks to months and response to sclerosing agents is poor.[39,58] When both the pleural fluid cytology examination and pleural biopsy are carried out in patients with far-advanced carcinoma of the pleura, the diagnostic yield approaches 90 percent.[42]

Tuberculous Pleurisy

Tuberculous pleural effusions often occur in the absence of radiographic evidence of pulmonary tuberculosis. The formation of pleural fluid is partly a result of hypersensitivity to tuberculin protein. A tuberculous effusion is usually straw colored (serosanguineous less than 20 percent of the time), with leukocyte counts less than 10,000 per μl and a mononuclear (lymphocyte) predominance.[13,45] A neutrophil-predominant effusion may be seen in acute tuberculous pleurisy. The presence of either a large percentage of mesothe-

lial cells[59] or eosinophils[13,17] in the pleural fluid makes the diagnosis of tuberculous pleurisy unlikely. Occasionally a low pleural fluid pH and low glucose level are found. The diagnosis of a tuberculous pleural effusion depends on: (1) a positive AFB stain of pleural fluid specimen (20 percent), (2) a positive pleural fluid culture for *Mycobacterium tuberculosis* (20 percent to 70 percent), (3) the finding of a caseating granuloma in pleural tissue (25 percent to 40 percent) or (4) culturing *M tuberculosis* from pleural tissue (55 percent to 80 percent).

Rheumatoid Pleurisy

Rheumatoid pleural effusions are most commonly found in men with rheumatoid nodules, active articular disease and high serum rheumatoid factors.[60,61] However, the effusion per se may produce no symptoms and may antedate clinical evidence of arthritis.[61]

The effusion is usually unilateral and it is rare for the interstitial lung disease or necrobiotic nodules of rheumatoid lung disease to be present. The effusion characteristically is present for months or years. The pleural fluid has a yellow to yellowish-green color and usually is turbid. The leukocyte count varies from several thousand to 20,000 per μl, with the cellular predominance depending on whether the presentation is acute or chronic. The LDH concentration is generally high (frequently more than 1,000 IU per liter). The pleural fluid characteristically has a glucose concentration of less than 30 mg per dl and a pH of around 7.00.[20,37,62] The mechanism for the low glucose concentration appears to be a selective block in glucose transport from blood to pleural space[63] and glycolysis by the pleural membrane.[27] Pleural biopsy usually reveals nonspecific inflammation but occasionally a rheumatoid nodule may be seen.

Pleural Effusions Associated With Pancreatitis

The exact incidence of pleural effusions associated with acute pancreatitis is unknown but probably approaches 10 percent.[64] The effusions are small to moderate in size and are usually left sided but may be bilateral or isolated to the right side.[64] The effusion is usually a serosanguineous exudate with a polymorphonuclear predominance and with amylase levels at least twice as high as the upper limit of the serum amylase level and higher than a simultaneously determined serum amylase level.

Treatment of Pleural Effusions

The treatment of a pleural effusion should be directed at the underlying cause. In all instances, with the exception of empyema and carcinoma, this does not involve direct manipulation of the pleural space. In an empyema, adequate drainage by chest tube must be established. The failure of a good clinical response in empyema is almost never due to the inability of antibiotic action to penetrate the pleural space but to inadequate drainage.[65] If this cannot be accomplished by chest tube and the patient remains septic, a thoracotomy needs to be done so that effective drainage can be accomplished.

In patients with intractable malignant effusions leading to dyspnea, producing pleural symphysis with chest tube drainage and instillation of a sclerosing agent usually are effective palliative measures. Excellent results with minimal morbidity in properly selected patients have been achieved with tetracycline hydrochloride.[66]

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Rheumatoid Arthritis

From Rubens to Restriction Maps

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *This Medical Staff Conference concerns rheumatoid arthritis. Dr. Jack Stobo is the discussant and his presentation is subtitled "From Rubens to Restriction Maps."*

DR. STOBO:† I will discuss some of the interesting recent concepts concerning the influence of genetically controlled immune reactivity on the expression of rheumatoid arthritis.

Background

In August 1800 a French medical student, Augustin Jacob Landre Beauvais, presented his thesis entitled "Should we recognize a new type of gout to be called primary asthenic gout?" The thesis described a previously unrecognized form of arthritis that clearly differed from gout in four ways: (1) The sex distribution was predominantly female; (2) those affected were indigent and asthenic, rather than wealthy and robust; (3) several joints rather than a single joint were involved, and (4) though the pains were less severe than gout, the attacks lasted much longer. Subsequently this constellation was accepted as representing a new form of arthritis, named rheumatoid arthritis by Sir Alfred Garrod in 1859.

In an attempt to determine the causes of rheumatoid arthritis, several investigators have studied the antiquity of the disease. If the reports by Landre Beauvais in 1800 indeed heralded the onset of rheumatoid arthritis, it might be argued that environmental factors, perhaps related to the industrial revolution, are etiologic. The studies tracing the disease's antiquity show that though osteoarthritis is clearly present in the fossil remains of dinosaurs, there is no evidence that these animals had rheumatoid arthritis. Osteoarthritis, gout and ankylosing spondylitis have been found in the mummified remains of persons who lived several thousands of years before Christ, but none of those remains have the characteristic features of rheumatoid arthritis. Moreover, whereas the Bible clearly describes many forms of arthritis, there is no description of anything resembling rheumatoid arthritis.

Recently it has been suggested that the earliest documentation of rheumatoid arthritis can be found in the paintings of the Flemish artist Peter Paul Rubens, who lived from 1577 to 1640.[1] In

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ABBREVIATIONS USED IN TEXT

HLA = human leukocyte antigen
Ir = immune response

the period from 1633 to 1635, Rubens painted the picture entitled *The Holy Family with St. Anne.* Notice the hand of St. Anne in this picture (Figure 1). There is dorsal swelling about the wrist, dorsal concavity of the hand, swelling at the metacarpophalangeal and proximal interphalangeal joints and swan-neck deformity of the fingers. In a later painting of St. Anne by Rubens, this deformity of the hand had worsened. These deformities and their worsening fulfill four of the American Rheumatism Association's criteria for the diagnosis of rheumatoid arthritis.

It appears that rheumatoid arthritis has indeed existed for only about 400 years. Based on this possibility, two major factors have been evoked as being causal in the development of the disease. The first is environmental influences. Perhaps something in the environment that appeared in the period 1600 to 1700 was related to the development of the disease. Exactly what this environmental factor could be is unknown. Second, it has been hypothesized that some infectious agent that appeared at this time is responsible. However, there has been no evidence that directly implicates a transmissible agent in the development of rheumatoid arthritis. Therefore, the significance of the finding that rheumatoid arthritis is a relatively new disease is obscure.

Genetic and Immunologic Factors

There may be other factors that, while perhaps not etiologic, play important roles in the disease. These include both genetic and immunologic factors. Support for genetic influence comes from the observation that rheumatoid arthritis may cluster within families, and that concordance for rheumatoid arthritis in monozygotic twins is higher than the concordance for rheumatoid arthritis in dizygotic twins. Support for a role for immunologic factors derives from the observation that various types of autoimmune reactivity (rheumatoid factor, for example) are present in patients with rheumatoid arthritis. I will present some recent observations that implicate both genetic and immunologic influences in the development of this disease. Specifically I will describe how the so-called immune response genes can regulate the development of a specific immune response that is required for the expression of rheumatoid arthritis.

During the past five years there has been renewed interest in the role of autoimmune reactivity

Figure 1.—Detail of St. Anne's hand from Rubens' *The Holy Family with St. Anne,* painted between 1633 and 1635. Reprinted with permission from the North Carolina Museum of Art, Raleigh, North Carolina.

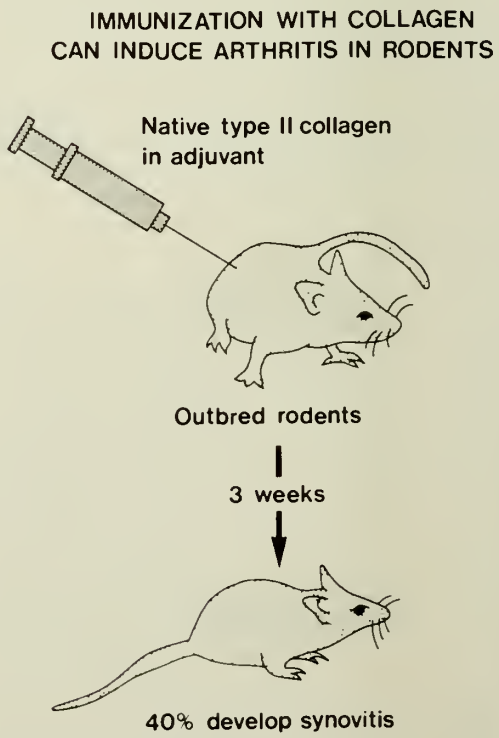

Figure 2.—Schematic for the induction of arthritis in rodents.

in the development of rheumatoid arthritis, specifically in the role of collagen as an antigen and the nature of the immune response to collagen in causing the synovitis. Collagen is a ubiquitous protein molecule that is present in almost every tissue in the body. It exists as a triple helix of three interwound polypeptide chains. In fact, there are several types of collagen, each of which has a different distribution in the body. For example, type I collagen is found predominantly in bone, tendon and arteries; type II collagen is present in the hyaline cartilage of joints; type III collagen is present in the skin and blood vessels, and type IV collagen is present predominantly in basement membranes. The hyaline cartilage, which contains type II collagen, plays an important role in preventing destruction of bone in the joint.

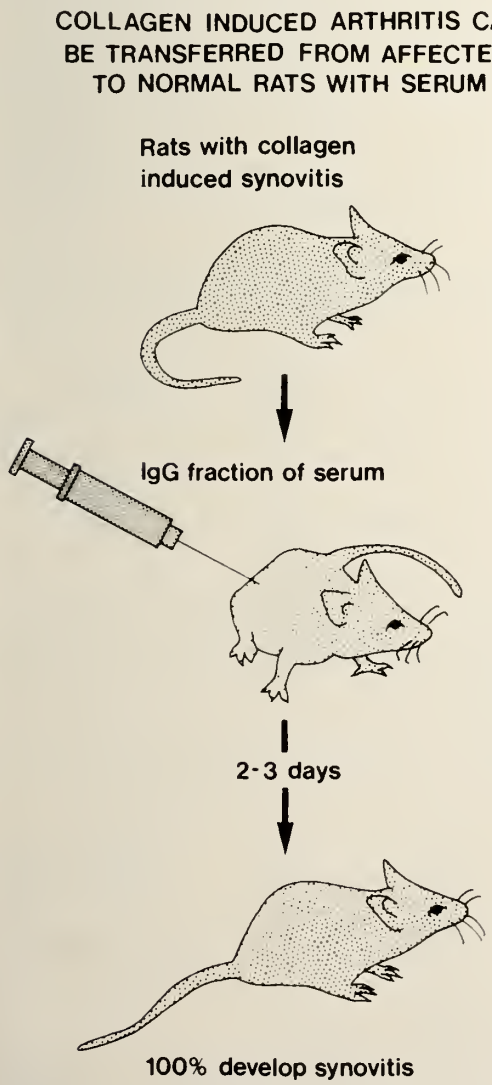

Figure 3.—Schematic for the passive transfer of arthritis in rodents.

The interest in the role of immune reactivity to collagen in the development of rheumatoid arthritis derives from the fact that a synovitis can be induced in rodents by immunizing the animals with collagen (Figure 2).[2-4] If outbred rats are immunized with native type II collagen in either complete or incomplete Freund's adjuvant, a synovitis that histologically and radiographically resembles rheumatoid arthritis will develop in approximately 40 percent to 50 percent of the animals. The collagen used for the immunization has to be type II collagen, the same type of collagen that is present in cartilage or joints.

It has been possible to transfer the synovitis from affected to nonaffected animals with serum.[5] A typical experiment of this type is depicted in Figure 3. In this experiment the investigators induced synovitis in rats by immunization with collagen. They then isolated the serum and fractionated it to obtain material that was enriched in IgG possessing a high titer of antibody to native type II collagen. This material was then transferred to normal rats and within two to three days a transient form of arthritis that again histologically and radiographically resembled the rheumatoid arthritis of humans developed in virtually all of the rats. These two observations suggest that immune reactivity to native type II collagen can be accompanied by a synovitis that resembles the synovitis seen in human rheumatoid arthritis. As indicated in Figure 2 if one immunizes outbred rodents with collagen, synovitis will develop in approximately half of the animals, suggesting that there is another factor that determines whether or not synovitis will develop in an animal upon immunization with collagen. Subsequently, it was shown that the propensity for experimentally induced synovitis to develop in rodents was controlled by the immune response genes in the major histocompatibility complex.[3,4] Before continuing it is necessary to digress and explain briefly what is meant by immune response genes.

Immune Response Genes

The 17th chromosome of mice contains a set of genes termed the H-2 complex (Figure 4). Genes within this complex contain the code for transplantation antigens. One locus in the H-2 region is the Ir (immune response) locus, which contains the immune response genes. These Ir genes determine whether or not an immune response to a specific antigen will develop in a given strain of mice. In other words, these genes determine

whether or not an individual strain of mice will have cell-mediated or humoral immunity in response to a challenge with a specific antigen. The human leukocyte antigen (HLA) region is homologous to the H-2 region of mice and is present on human chromosome 6 (Figure 4). Genes in the HLA region also code for transplantation antigens. This region has three major subregions, the HLA-A, the HLA-B and the HLA-D loci. From several studies it appears that genes in the HLA-D locus represent the human equivalent of the mouse immune response genes.[6] The HLA-D genes determine whether or not a person will have an immune response to a specific antigen. The products of genes in the HLA-D locus are glycoproteins that are seen on the surface of only certain cells, including macrophages, B cells and activated T cells. The products of the HLA-D genes consist of a two-chain molecule, an α-chain that has a relatively high (35,000 daltons) molecular weight and a smaller β-chain (28,000 daltons). These molecules can be depicted by specific antisera and, when assayed by serologic tests, are called HLA-DR (D-related) determinants. There are at present ten HLA-DR determinants that can be detected with specific antisera and these are denoted as HLA-DR1 through HLA-DR10.

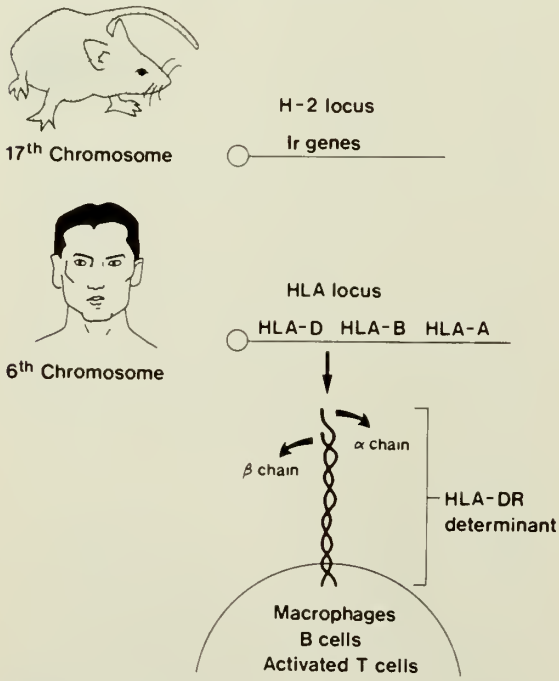

Figure 4.—Immune response genes depicted in the major histocompatibility complex of mice and humans. They are components of their respective major histocompatibility complexes. Ir = immune response, HLA = human leukocyte antigen.

As indicated in Figure 2, if one immunizes outbred strains of rodents with collagen, synovitis will develop in only some of them. Using strains of mice that are identical except for differences in their Ir genes, it can be shown that the ability of injected collagen to induce synovitis is controlled by the Ir genes.[3] These experiments are summarized in Table 1. Three points can be made from these data. First, not all strains of mice produce anticollagen antibodies when immunized with collagen. Only the H-2^q, H-2^b and H-2^d strains make relatively high titers of antibodies to collagen. Second, arthritis occurs only in strains of mice that produce anticollagen antibodies. For example, synovitis did not develop in H-2^k, H-2^j and H-2^p mice, which did not make substantial amounts of anticollagen antibodies. Third, synovitis develops in only some of the mice that produce anticollagen antibodies. To summarize, the immune response to collagen in mice is controlled by immune response genes. More important, though immune reactivity is a necessary condition for the development of arthritis, it is not by itself sufficient. It is possible for an immune reactivity

TABLE 1.—*Immune Response (Ir) Genes, Collagen Antibodies and Collagen-Induced Synovitis in Mice**

H-2 Haplotype	*Level of Collagen Antibodies µg/ml*	*Incidence of Synovitis percent*
Q	450	50-75
K	110	0
J	75	0
P	80	0
B	500	0
D	525	0

*The alphabetical notation of H-2 haplotype indicate strains of mice that differ only in their H-2 genes. These strains were immunized with type II collagen and then assayed for circulating titers of collagen antibodies and the percentage of mice that developed synovitis. Adapted from Wooley et al.[3]

TABLE 2.—*Frequency of HLA-DR Types in Normal Subjects and in Patients With Rheumatoid Arthritis**

HLA-DR Type	*Frequency in*	
	Normal Subjects Percent	*Patients With Rheumatoid Arthritis Percent*
DR1	15	25
DR2	26	22
DR3	13	21
DR4	19	60-80
DR5	27	13
DR7	30	13

*Normal controls and patients with rheumatoid arthritis were analyzed for the presence of six HLA-DR determinants. Results are presented as the percentage of individuals who are positive for a specific HLA-DR determinant. The data here are summarized from many studies.

to collagen to be noted in a mouse in which synovitis does not develop.

Immune reactivity to collagen, controlled by immune response genes, appears to contribute also to the synovitis seen in rheumatoid arthritis. As indicated in Figure 4, products of human immune response genes are displayed on the surface of lymphocytes and, when detected by antisera, are called HLA-DR antigens. As shown in Table 2, persons with rheumatoid arthritis have immune response genes that code for the production of a particular HLA-DR antigen, HLA-DR4. Whereas the lymphocytes of 19 percent of normal people show HLA-DR4, of patients with rheumatoid arthritis fully 60 percent to 80 percent show the

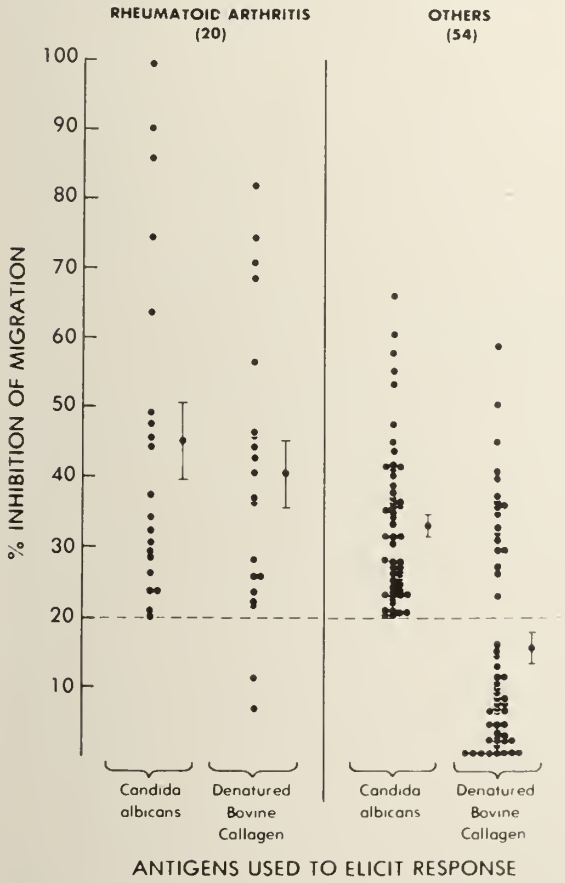

Figure 5.—Diagram of reactivity of peripheral blood mononuclear cells from patients with rheumatoid arthritis and controls to *Candida albicans* and denatured bovine collagen. Peripheral blood mononuclear cells from 20 patients with rheumatoid arthritis and 54 persons with either other forms of synovitis or no synovitis were compared for the synthesis of leukocyte inhibition factor in response to challenge with *C albicans* or denatured bovine collagen. Results are presented as percentage of inhibitors of migration. Values of more than 20 percent inhibition of migration indicate a positive response.

same HLA-DR antigen. This association between rheumatoid arthritis and HLA-DR4 can be found not only in whites, but also in American blacks and in Japanese.

Based on this observed association between rheumatoid arthritis and HLA-DR4, studies were initiated in our laboratory two years ago to determine whether or not patients with rheumatoid arthritis also show immune reactivity to collagen and whether this immune reactivity was determined by immune response genes linked to those coding for HLA-DR4.[7] In the first series of studies (see Figure 5), peripheral blood mononuclear cells from 20 patients with rheumatoid arthritis and from 54 controls (people with other forms of arthritis, such as osteoarthritis, or normal laboratory volunteers) were tested for immune reactivity to a control antigen, *Candida albicans,* or the experimental antigen, denatured bovine collagen. Immune reactivity was determined by assaying the ability of each antigen to induce the production of a specific lymphokine, leukocyte inhibitory factor, by T cells. The activity of the lymphokine was determined by measuring its ability to inhibit the migration of polymorphonuclear leukocytes. Synthesis of leukocyte inhibitory factor sufficient to cause more than 20 percent inhibition of migration indicates that immune reactivity is present, whereas amounts of the lymphokine that cause less than 20 percent inhibition of migration indicate that immune reactivity is absent.

The first item to note from these data is that the patients with rheumatoid arthritis and the controls showed immune reactivity to the control antigen, *C albicans.* Second, 18 out of the 20 patients with rheumatoid arthritis showed immune reactivity to collagen. Third, although when considered as a group the controls showed a mean reactivity to the collagen that would be considered negative, 18 of the 54 controls showed positive reactivity to the collagen antigen. Ten of these 18 controls were normal laboratory volunteers without any evidence of synovitis.

These studies indicate that though reactivity to collagen exists in a high proportion of patients with rheumatoid arthritis, collagen reactivity can also be found in persons who do not have any arthritis. We next asked whether or not there is any association between the presence of collagen reactivity and HLA-DR4. The lymphocytes from 28 collagen responders and 27 collagen nonresponders consisting of patients with rheumatoid

arthritis and normal persons were assayed for the display of the HLA-DR4 determinant (Table 3). Note that 21 of the 28 collagen responders were HLA-DR4-positive, whereas only seven were HLA-DR4-negative. Fifteen of the collagen responders were normal subjects and 11 of this group were HLA-DR4-positive. All of the HLA-DR4-positive persons, whether normal subjects or patients with rheumatoid arthritis, are collagen responders. Statistical analysis of these data shows that there is a significant ($P<.001$) association between the HLA-DR4 positivity and immune reactivity to collagen. Therefore, genes linked to those coding for HLA-DR4 do indeed appear to constitute immune response genes for collagen reactivity.

Based on these studies, we suggest the following scheme (Figure 6): During its physiologic degradation everyone is exposed to collagen. In people who are HLA-DR4-negative and thus lack the collagen immune response genes, this exposure does not result in immune reactivity to collagen.

TABLE 3.—*Association Between Collagen Reactivity and HLA-DR4**

	Collagen Reactivity			
	Responders		Nonresponders	
	Patients With RA	Normal Subjects	Patients With RA	Normal Subjects
HLA-DR4 Type + ..	10	11	0	0
− ..	3	4	2	25
TOTALS ..	28		27	

*Fifteen patients with rheumatoid arthritis (RA) and 40 normal persons were assayed for the production of leukocyte inhibitory factor in response to an in vitro challenge with collagen and for the presence or absence of the HLA-DR4 determinant. In responders collagen induced the synthesis of leukocyte inhibitory factor in a sufficient amount to cause more than 20 percent inhibition of neutrophil migration. + = positive, − = negative.

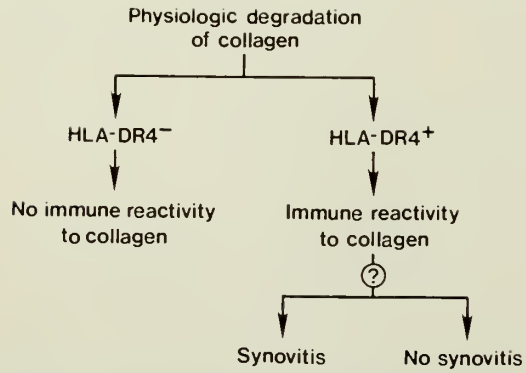

Figure 6.—Proposed model for the relationship between collagen reactivity, immune response genes and rheumatoid arthritis in humans.

However, in people who are HLA-DR4-positive and therefore contain the genes for a collagen immune response, immune reactivity to collagen occurs. A synovitis of rheumatoid arthritis will develop in a portion of those patients, but in most of these collagen responders, synovitis will not develop. This, then, is similar to the situation seen in rodent models of collagen-induced synovitis where immune reactivity to collagen constitutes a necessary but insufficient condition for the expression of synovitis.

A crucial question concerns the factors that determine in which of the collagen responders rheumatoid arthritis will develop. One possibility is that there are small but important differences in the HLA-DR4-linked genes that determine the expression of rheumatoid arthritis. The antisera used to detect HLA-DR determinants are relatively crude and therefore might not detect subtle differences in gene products. One approach to testing this hypothesis is to produce a monoclonal antibody that will detect antigenic differences in HLA-DR4 molecules. Another approach is to examine differences that exist in the immune response genes themselves. Recently it has been possible to obtain molecular probes capable of hybridizing to the DNA sequences of the human immune response genes, making it possible to examine the structure of these genes. Using such probes it will be possible to determine whether there are polymorphic differences in the immune response genes of HLA-DR4-positive persons in whom rheumatoid arthritis develops when compared with immune response genes in HLA-DR4-positive individuals in whom it does not. This type of analysis can use restriction endonuclease mapping to look for what has been termed "disease-associated genes." For example, one could extract DNA from the cells of an HLA-DR4-positive normal individual and DNA from an HLA-DR4-positive patient with rheumatoid arthritis. The DNA could then be digested with restriction endonucleases, fractionated by gel electrophoresis and hybridized with a probe specific for HLA-DR4-associated immune response genes. By noting differences in the size of DNA fragments that hybridize with the probe, it may be possible to determine subtle differences in the DNA sequence of immune response genes associated with the development of rheumatoid arthritis. It should be emphasized that this approach is associated with many variabilities that could pose real problems in the interpretation of the results. In addi-

tion, this technique may not be sensitive enough to detect subtle but important differences in the amino acid structure of HLA-DR determinants.

Summary

Rheumatoid arthritis is a relatively modern disease that was first depicted in patients in the paintings of Rubens during the early 17th century. The etiology of the disease is still unknown. However, it appears that immune reactivity to collagen, which is controlled by immune response genes, is important in the expression of synovitis. The potential for dissecting polymorphisms in immune response genes should provide useful information for determining the precise role that immune response genes play in the development of rheumatoid arthritis.

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Award for Scientific Writing

ENTRIES FOR THE JEAN SPENCER FELTON, MD, AWARD for excellence in scientific writing are now being solicited by the Western Occupational Medical Association. The award is made annually by WOMA to the author of a book, journal article or other written work important to the field of occupational health. Mail copy of written piece being submitted for judging to Joseph LaDou, MD, 433 Palmer Avenue, Aptos, CA 95004. The only entry stipulation is that authors must reside in the western states. The deadline for entries is September 15, 1982.

Important Advances in Clinical Medicine

Epitomes of Progress — Allergy

The Scientific Board of the California Medical Association presents the following inventory of items of progress in allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in allergy that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Aspirin Desensitization in Rhinosinusitis Asthma

Approximately 10 percent of all asthmatic patients (30 percent to 40 percent of asthmatic patients with rhinosinusitis with or without nasal polyps) are sensitive (intolerant) to aspirin. This form of asthma is characterized by persistent eosinophilic inflammation of respiratory tract mucous membranes, which is independent of aspirin exposure. The severity of aspirin-induced reactions is dose-dependent. The reactions are characterized by rhinorrhea, conjunctivitis, periorbital swelling, bronchospasm and, occasionally, flushing, abdominal pain and hypotension. Cross-reactivity to indomethacin is virtually 100 percent, whereas cross-reactivity to other nonsteroidal, antiinflammatory drugs is variable. For this class of drugs there is a rough correlation between effectiveness of prostaglandin cyclooxygenase inhibition and the degree of cross-sensitivity. Tartrazine, which does not inhibit prostaglandin synthesis, nevertheless is reported to cross-react in approximately 10 percent of aspirin-sensitive patients.

Treatment of aspirin-sensitive rhinosinusitis asthma is pharmacologic, as avoidance of aspirin does not change the course of the disease. Corticosteroids administered either systemically or topically, or both, are frequently necessary to control upper and lower airway pathology. Sinus roentgenograms are abnormal in 75 percent to 95 percent of aspirin-sensitive patients, frequently showing pansinusitis. In most instances, however, the radiologic abnormalities are the consequence of the underlying disease and do not represent bacterial sinus infection. Sinus drainage surgical procedures and polypectomies are often unrewarding due to rapid recurrence of hypertrophic rhinosinusitis and polyp formation.

A relatively new procedure of aspirin desensitization may be of help both in identifying basic biomolecular mechanisms and as a therapeutic manipulation. In aspirin-sensitive patients who might benefit from treatment with aspirin or nonsteroidal antiinflammatory drugs for another condition (headache, arthritis, thromboembolic prophylaxis), aspirin desensitization and continued daily treatment with aspirin is now feasible. The

use of aspirin for treatment of rhinosinusitis and asthma is currently undergoing further evaluation.

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Exercise-Induced Anaphylaxis

ANAPHYLAXIS IS AN ACUTE, potentially fatal, multisystem reaction characterized by urticaria, angioedema, bronchospasm, hypotension and abdominal cramps. In most cases the reaction is caused by IgE antibody-mediated release of histamine and SRS-A (slow-reacting substance of anaphylaxis), which increase vascular permeability and cause contraction of smooth muscle in the target organs. The allergen is most often a food, drug or insect venom. Non-IgE antibody-mediated activation of vasoactive peptides, kinins or complement-derived anaphylatoxins C5a or C3a might play a role in some instances of anaphylaxis. *Anaphylactoid* reactions refer to nonimmunologic release or activation of mediators such as occurs in the systemic reactions to aspirin or iodinated radiographic contrast media.

The allergen causing anaphylaxis is usually readily apparent from the rapid onset of symptoms following exposure. If the cause is not obvious from the initial evaluation, careful follow-up with appropriate tests will reveal the responsible allergen in most cases. Nevertheless, some patients have recurrent episodes of anaphylaxis that are idiopathic.

Anaphylaxis in athletes, induced by physical exercise, was recently described. The symptoms and signs of the reaction are identical to those in allergen-induced anaphylaxis and are severe enough in some cases to be considered life-threatening. Most of these persons are in their late teens or early 20's, and in some cases frequent attacks had occurred over a number of years. A personal or family history of atopic disease is common but not universal in this group of patients.

The mechanism of exercise-induced anaphylaxis and its relationship to cholinergic urticaria are unknown. The latter condition is characterized by the appearance of small cutaneous wheals with itching following exercise, overheating or emotional stress. Two patients with exercise-induced anaphylaxis had skin lesions typical of cholinergic urticaria, hypotension, angioedema and elevation of plasma histamine levels during an attack. In patients with exercise-induced anaphylaxis, however, symptoms are not precipitated by heat or stress.

Exercise-induced anaphylaxis does not appear to be related to exercise-induced asthma, a characteristic feature in nearly all asthmatic patients. Most patients with exercise-induced anaphylaxis have no history of asthma.

Treatment with epinephrine, antihistamines and fluid replacement appears to be as effective in this condition as in the allergic form of anaphylaxis. Pharmacologic preventive measures have not yet been evaluated. Regular, repeated exercise by one patient resulted in progressive diminution of symptoms and in vivo histamine release, although similar attempts at exercise "desensitization" in other patients have been unsuccessful. Until the cause of exercise-induced anaphylaxis is clarified, patients should modify their exercise program to minimize the recurrence of these reactions.

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Standardization of Allergens

STANDARDIZED EXTRACTS of allergens should have lot-to-lot consistency and contain the allergens responsible for eliciting an allergic response. In general, such extracts will have a labeled potency and will be equivalent to a reference preparation. The expiration date for standardized extracts is established by stability studies and varies with the concentration.

The need for standardization has been amply shown by published studies describing as much as a thousandfold variation in skin test reactivity among commercial extracts. Extracts of low potency are not necessarily low in allergen content but may be lacking one or more important allergens or may contain badly degraded allergens. Consequently, using nonstandardized extracts can

result in misdiagnosis and almost certainly will result in reduced immunotherapeutic efficacy.

Although a number of methods are potentially useful, those with the most promise for standardization include specific antigen analysis and radioallergosorbent test (RAST) inhibition. Isoelectric focusing, although not quantitative, is a simple physicochemical procedure that provides a graphic demonstration of the quality and identity of an extract and is especially valuable with pollen extracts. The in vitro methods derived from quantitative skin testing have been shown to correlate with a relative potency.

Currently, extracts of venoms of stinging insects are standardized as well as extracts of short-ragweed pollen. Before 1983 a number of other standardized extracts should become available, including extracts for use in pollen and cat allergy. The standardized extracts will not only improve the practice of allergy but will aid investigations into fundamental aspects of allergic disease.

Standardized extracts should permit interchangeability of extracts from one manufacturer to another. In some instances, these extracts may be more potent or reactive than currently available extracts and may have an earlier expiration date, especially for high dilutions.

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Immunologic Benefits of Breast Feeding

RESULTS OF NUMEROUS clinical and laboratory studies leave little doubt that human milk is best for infants and especially so in families with allergies. Colostrum provides a neonate with a concentrated dose of antibodies, stimulates the passage of meconium and thereby the excretion of bilirubin, and helps establish nonpathogenic *Lactobacillus bifidus* as a predominant organism of the gastrointestinal flora.

Mature breast milk is the ideal nutrient during infancy. A predominance of whey protein results in a soft, digestible curd. The amino acid content is especially appropriate for rapid growth. Lipid digestion and absorption, facilitated by the presence of lipases, is nearly complete. Minerals such as iron are more bioavailable. The renal solute load is low, providing a substantial margin of safety while kidney function is maturing.

The continuing presence of immunoglobulins, a number of nonspecific antiinfective factors including lysozyme, lactoferrin, interferon, complement and the bifidus factor, as well as viable cellular components, offer an important passive protection against enteric and respiratory pathogens. Additionally, penetration of the immature gastrointestinal mucosal barrier by potentially allergenic antigens is inhibited by substances in breast milk.

Bonding and healthy psychological development are naturally promoted by the frequent physical contact and reciprocal neuroendocrine interaction between a nursing mother and infant. There are neuroendocrine reflexes that are also beneficial to maternal health. Oxytocin, responsible for the milk-ejection reflex, stimulates uterine contractions, which decrease postpartum bleeding and facilitate uterine involution. Elevated prolactin levels delay the return of ovulation and menstruation.

Because of the many benefits, breast-feeding should be actively encouraged among expectant parents. Ideally nursing should continue for as much of the first year of life as possible, with gradual introduction of solid foods after the fifth or sixth month. For families with allergies, exclusive breast-feeding with attention to the nursing mother's diet appears to delay or prevent allergic diseases in offspring.

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Monoclonal Antibodies

IN 1975 Milstein and Köhler, while studying the genetic regulation of antibody synthesis in mice, described a technique of fusing together normal antibody-producing cells and myeloma cells. Some of the resulting hybrid cells acquired two highly desirable characteristics: continuous replication typical of the myeloma cell and synthesis of antibody specified by the normal B cell. These fused cells can be grown as clones of a

single cell, and the resulting clone is termed a hybridoma. Hybridomas may be maintained in Petri dishes and antibody harvested from the supernatant. Alternatively they can be reinserted into the peritoneal cavity of a mouse and the antibody-rich peritoneal fluid withdrawn. Both methods can produce monospecific antibody in relatively large amounts.

Monoclonal antibodies have already had a major impact on biomedical research and are beginning to improve both laboratory and clinical medicine. In vitro diagnostic assays in which polyclonal antibodies have been used in the past, for example, radioimmunoassay and enzyme immunoassay, are more and more incorporating monoclonal technology. The first kit using a monoclonal antibody approved by the Food and Drug Administration was for a radioimmunoassay to measure serum IgE. Other kits will be available soon, including one using a monoclonal antibody to measure serum theophylline concentrations. A higher degree of quality control will exist because a permanent source of a monospecific antibody reagent is now possible. Monoclonal antibodies are also being developed against drugs, hormones, microbial antigens and proteins and will soon become part of routine hospital diagnostic repertoires.

Monoclonal antibodies specific for tumor antigens conjugated with short-lived radionuclides are being developed for in vivo cancer detection. Such an antitumor antibody by itself or conjugated to chemotherapeutic agents has proved useful in treating cancer in laboratory animals and phase I and II trials in humans are underway. A monoclonal antibody for the cytotoxic lymphocyte that causes renal graft rejection has been used to stop rejection episodes.

Because antibodies can be developed that eliminate lymphocytes responsible for graft versus host disease, transplantation across histocompatibility barriers may be possible. Removal of these cells from bone marrow, and transplantation of the depleted marrow elements into lethally irradiated cancer patients is being investigated for the treatment of otherwise fatal leukemias. In drug overdose (for example, theophylline, digoxin) these antibodies can be used to rapidly reduce toxic serum concentrations. There is no field of medicine, either in vivo or in vitro diagnostics, or in vivo therapeutics, that will not be affected by monoclonal antibody technology.

Potential allergic reactions to murine monoclonal antibodies must be kept in mind because the administration of foreign protein can cause both serum sickness reactions and IgE sensitization. Radioallergosorbent test (RAST) for IgE antimurine protein is not available, but skin testing with the relevant monoclonal antibody should point to IgE-mediated reactions.

In fewer than seven years the technique of cell fusion has been developed for practical application. All physicians will need to be knowledgeable about this exciting advance in the evaluation and care of patients.

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Immunoglobulin Subclass IgG4 Deficiency

ELECTROPHORETICALLY fast-moving IgG homocytotropic antibodies are known to play a role in local anaphylactic reactions in rodents and have been suspected of being important in human hypersensitivity reactions. Antibodies of the subclass IgG4 are the most likely candidates in humans. The development of a radioimmunoassay specific for IgG4 has made it possible to measure IgG4 levels in humans of all ages. A number of persons have been found with definitely elevated levels of IgG4 (above 1,000 μg per ml, or 100 mg per dl). Nearly all of these have proved to be highly allergic people and some have had high levels of antigen-specific IgG4 antibodies but no increase in total or antigen-specific IgE.

In one report four persons who had an apparent absence of IgG4 (serum levels below 1 μg per ml) were discussed. Since that initial report eight more persons have been found with profound deficiency of serum IgG4. Eleven of these patients have had a syndrome of severe recurrent infections of sinuses, middle ear and lungs. Recurring pneumonia, often associated with bronchiectasis, constitutes the most ominous finding. We estimate that in 20 percent to 25 percent of persons with "idiopathic" bronchiectasis there is an isolated deficiency of IgG4.

In addition, persons with IgA deficiency or common variable immunodeficiency with recurrent pneumonia, bronchiectasis (or both) frequently have an absence of detectable IgG4,

whereas those with nonsymptomatic IgA deficiency have normal IgG4. Because IgG4 deficiency is almost universal in symptomatic IgA deficiency and similar symptoms are found in patients with an isolated deficiency of IgG4, it is likely that IgG4 plays an even more critical role than IgA in the immunologic defense mechanisms of the respiratory tract.

Two patients with primary or idiopathic pulmonary hemosiderosis were found by our laboratory to have an isolated deficiency of IgG4, suggesting that this immunoglobulin may be important to the integrity of the pulmonary alveolar capillary wall. It is known that receptors for IgG4 are present on basophils, neutrophils, platelets and mast cells. The precise manner in which IgG4 plays its role in maintaining a healthy respiratory tract is unknown, but presumably tiny amounts are sufficient. In one family we studied, a mother and daughter have severe recurrent respiratory tract infections and bronchiectasis associated with an isolated absence of IgG4 (levels below 1 μg per ml). A second daughter who is healthy has definitely subnormal but detectable levels (2 to 4 μg per ml). Of healthy persons, 95 percent have levels of over 15 μg per ml, and the mean level of healthy controls is 250 μg per ml.

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Metabisulfite Sensitivity as a Cause of Asthma

RECENTLY FOUR asthmatic patients have been identified who seem acutely sensitive to the levels of potassium metabisulfite that are frequently found in restaurant meals. The patients have in common a history of sudden onset of severe wheezing, chest tightness, flushing and weakness following ingestion of restaurant foods, particularly wines, salads and avocado dips.

These patients all have the features of chronic steroid-dependent asthmas, rhinosinusitis, nasal smears negative for eosinophils and normal total serum IgE levels. None of them have been found to have type I reagin-mediated reactions to metabisulfite via direct skin testing or histamine release from their peripheral basophils. All four had severe bronchospasm when challenged with between 10 and 50 mg of metabisulfite given orally. One improved when placed on a diet eliminating potassium metabisulfite.

A variety of sulfiting agents, including sulfur dioxide and several inorganic sulfites, have been used for centuries in food processing. These agents are currently used as sanitizers for food containers and fermentation equipment, preservatives to reduce or prevent microbial spoilage of foods, selective inhibitors of undesirable microorganisms in the fermentation industry and antioxidants and inhibitors of enzyme-catalyzed oxidative discoloration and nonenzyme browning that often accompanies the preparation, storage and distribution of foods. It has been shown that in rats fed thiamine-deficient diets, toxicity and death resulted from administration of sodium sulfite in doses of 50 mg per kg a day. However, with a proper amount of thiamine in the diet, the rats survived doses of over 300 mg per kg a day.

Currently the Food and Drug Administration allows the addition of sulfites to nonthiamine-containing foods and drinks without any disclosure or restrictions. Potassium and sodium metabisulfite, as well as sulfur dioxide, are commonly added to fresh fruits and vegetables, shellfish, beer and wine. Estimates are that 2 to 3 mg of sulfites are consumed each day by the average person in the United States and 5 to 10 mg of sulfite can be consumed by those who are regular drinkers of beer and wine. The highest concentrations occur in restaurant salads, vegetables, potatoes and avocado dip. A person can ingest 25 to 100 mg of metabisulfite in one restaurant meal.

A case of anaphylaxis after ingestion of sodium bisulfite was reported. The patient's symptoms consisted of generalized urticaria, angioedema of the tongue and constriction of the chest. This patient had detectable reagin as evidenced by a positive Prausnitz-Küstner reaction with sodium bisulfite solution. This is in contrast to the four patients recently described. There are several possible explanations for this reaction, such as complexing of potassium metabisulfite with serum or tissue proteins to produce a complete antigen. Metabisulfite metabolites could be the responsible substances, acting as haptens, antigens or as nonreaginic anaphylactoid reactants. Another mechanism might involve reactions through the

cholinergic reflex arc. This hypothesis is especially attractive because it is known that inhaled sulfur dioxide activates tracheobronchial irritant receptors that in turn stimulate the afferent arc of the cholinergic reflex. All sulfites are converted to sulfur dioxide in solution. The mechanism of susceptibility to metabisulfites in these patients, however, remains obscure.

Metabisulfite sensitivity probably is not rare. A history of anaphylaxis occurring following ingestion of restaurant food and drink, particularly salads and avocado dip, suggests that metabisulfite sensitivity reactions have occurred. Anaphylaxis after ingestion of soft drinks with sulfur dioxide or wines; shrimp or other seafood, or restaurant potatoes or vegetable combinations sprayed with potassium metabisulfite solutions should alert a physician to the possibility of this syndrome.

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Urticarial Vasculitis

URTICARIA IS CHARACTERIZED clinically as pruritic, erythematous, cutaneous elevations arising from dilated blood vessels and areas of cutaneous edema. After intradermal injection, many mediators of inflammation are capable of producing lesions that resemble urticaria. These mediators include histamine, the anaphylatoxins of complement (C3a, C4a and C5a), certain leukotrienes, some prostaglandins and perhaps serotonin.

Inflammation within blood vessels is called vasculitis and may appear as the consequence of one or more mechanisms. As detected by routine histologic and immunofluorescence techniques, vasculitis is frequently found in acute urticaria precipitated by adverse drug reactions, hepatitis B infection or serum sickness due to heterologous protein administration. Vasculitis is less frequently observed in the specimens from skin biopsies of patients with chronic idiopathic urticaria. However, recent investigations clearly show characteristic histologic or plasma complement abnormalities, or both, in some patients with chronic idiopathic urticaria.

Although mild inflammatory changes of vasculitis are detected in the specimens from skin biopsies of many patients with chronic idiopathic urticaria, the patients with chronic urticaria and necrotizing venulitis and others with hypocomplementemic vasculitic urticarial syndrome constitute distinct subsets of urticarial patients with more prominent systemic features and more severe vasculitis. Necrotizing venulitis was observed in adults with recurring urticaria, episodic arthralgias or arthritis, abdominal pain or glomerulitis. The plasma complement analyses in some of these patients indicated activation of the classical pathway of complement as shown by decreased total hemolytic complement (CH_{50}), Clq, C4 and occasionally C3. In other patients the complement analyses were normal.

The other syndrome, called the hypocomplementemic vasculitic urticarial syndrome or systemic lupus erythematosus (SLE)-related syndrome, was observed in adult women who have persistent urticaria, leukocytoclastic angiitis, severe angioedema, arthralgias, arthritis, neurologic complications, sensitivity to potassium iodide and profound hypocomplementemia. The complement analyses of these patients' plasmas showed depressed CH_{50}, C4, C2 and C3 in association with deficiency of Clq. The deficient Clq apparently relates to the presence of an unusual immunoglobulin that precipitates Clq (7S Clq precipitin or low molecular weight Clq precipitin). Both the Clq deficiency and the 7S Clq precipitin are characteristic of this syndrome.

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Rhinitis

INFLAMMATION OF THE nasal mucosa is commonly termed rhinitis. There are a number of causes. A diagnostic classification can be based on more specialized nasal evaluations including nasal cytology, rhinomanometry, nasal challenge, and olfactory and ciliary function testing.

Nasal cytology is carried out by gently scraping the mucosal lining of the inferior turbinate with a calcium-alginate applicator and placing the specimen on a glass slide. The prepared slide is then metachromatically stained and the cell pattern examined microscopically. Nasal airway resistance

TABLE 1.—*Classification of Nasal Disorders Based on Systematic Evaluation*

- Inflammatory rhinitis
  - Eosinophilic allergic rhinitis
    - seasonal
    - perennial
  - Eosinophilic nonallergic rhinitis
  - Infectious rhinitis
    - viral
    - bacterial
  - Nasal polyps
  - Nasal mastocytosis
  - Atrophic rhinitis
- Noninflammatory rhinitis
  - Vasomotor rhinitis
    - associated with local or systemic condition
    - autonomic dysfunction
  - Rhinitis medicamentosa
- Structure-related rhinitis

can be measured by an active, single-nostril anterior rhinomanometric technique. Simultaneous recording of pressure and flow rate allows calculation of resistance. This determines the degree of reversible and fixed nasal obstruction when done before and after topical administration of a decongestant. This technique can also be used to record changes in nasal patency following allergic or chemical challenges and drug therapy. To evaluate for anosmia or hyposmia, the threshold for detecting inhaled pyridine is determined. Ciliary function is most simply tested after placing a small particle of saccharin on the anterior portion of the inferior turbinate. Elapsed time is recorded until a sweet taste is noted by the patient. Structural and functional abnormalities of cilia will prolong the time interval from placement to taste.

On the basis of this systematic evaluation, nasal disorders can be classified, as shown in Table 1. It should be noted that many of these categories can coexist, and may be acute or chronic in nature.

Organizing an approach on which to base clinical and laboratory findings can assist us in understanding these disorders and direct our continued research into their pathogenesis. Such an approach can place each rhinitis patient in a functional classification that suggests specific therapy. Similar methods have assisted the development of diagnostic and treatment criteria for lower airway diseases. Thus we can anticipate progress in the care of patients with rhinitis.

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Seminal Fluid Allergy

URTICARIA AND HYPERVENTILATION after coitus have occasionally been reported to physicians, who attributed such reactions to psychic agitation. However, a case has been reported of a woman who had anaphylactic shock consisting of angioedema, wheezing, "uterine pain" and cardiovascular collapse within minutes of coitus. A glycoprotein fraction of seminal plasma was identified as the antigen. Diluted to 10^{-6} it caused a positive reaction on direct skin tests; her serum caused a positive reaction on passive transfer tests. Since this initial case there have been sporadic reports of anaphylaxis due to semen. Levine and co-workers reported the case of a patient who had anaphylaxis, positive findings on skin tests and leukocyte histamine release (LHR) with a 20,000 to 30,000 molecular weight (mol wt) fraction of seminal plasma, but not of sperm extract. Her leukocytes reacted with this fraction of semen from seven different men tested.

IgE-antibody involvement in such cases has been found by radioallergosorbent test (RAST) with seminal fluid fractions. We have seen a patient who three times had anaphylaxis necessitating epinephrine; she also had a concomitant severe flare of her eczema. Immunotherapy with a dilution of her husband's semen has been attempted. Condom usage by the patient's husband has prevented subsequent reactions, except on two episodes of "condom tear accidents" when she had localized urticaria. RAST and LHR values fell during absence of exposure, only to rise abruptly after each accident.

Of four patients reported by Bernstein and associates, two had anaphylaxis that required epinephrine and two had only genital tissue edema and burning pain. Both women with anaphylaxis had positive reactions on skin tests, RAST and LHR. One had her first episode on first coitus after childbirth, as did our patient; a disrupted vaginal mucosa may add risk to such sensitization. The two women with severe localized reactions had positive findings on lymphoproliferation and leukocyte migration inhibition assays with both sem-

inal plasma and sperm extract, suggesting cellular immunity to semen. Two couples had a remarkable sharing of histocompatibility (HLA) antigens that suggested another possible predisposing factor to seminal sensitization, as has been suggested earlier for fertility problems. Although these reactions are considered rare, milder localized forms may mimic other female pelvic inflammatory conditions.

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EDITORIALS

WJM Welcomes WMS

At its meeting at the Jackson Lake Lodge, Moran, Wyoming, June 30 through July 3, the House of Delegates of the Wyoming Medical Society (WMS) voted to become the seventh western state medical association to make The Western Journal of Medicine its official journal. The members of WMS will now receive it as a benefit of their membership. The decision of the House followed a six-month period during which the membership of WMS received the journal on a trial basis. The editors are pleased that its value to the membership was attested by the action of the House.

The WJM seeks to be a truly useful journal for its readers, the greatest number of whom are practitioners. It seeks to offer a variety of fare that also will include something of interest for students, academicians, researchers and even political leaders of our profession—of whom there are many among its readers. It seeks to reflect the vitality and achievements in science, education and practice that are hallmarks of medicine in the West, and to give these a stronger presence in the medical literature. The editors, the editorial board and many others are dedicated to making this journal a regional instrument of physician education and continuing education in the West, and also an increasingly distinguished journal on the national scene.

We welcome the Wyoming Medical Society to the WJM family of associations and its members to our readership. We look forward to a long and productive association which should be of great benefit to all concerned.

—MSMW

Further Comments on Pleural Effusions

The presence of a pleural effusion raises many diagnostic and therapeutic questions. In this issue Steven A. Sahn has provided an excellent review of this subject.

Table 2 of Dr. Sahn's article outlines the more common causes of pleural effusions and classifies each as to whether it is more commonly a transudate or an exudate. As indicated in this table there are more diagnostic possibilities for an exudative than for a transudative effusion. Further, the diseases that cause a transudate (such as congestive heart failure, cirrhosis with ascites, the nephrotic syndrome and hypoalbuminemia) usually present a clear clinical picture with supportive historical, physical and laboratory data. Exudative effusions, by comparison, may present more difficult diagnostic and therapeutic issues. The features of three of the more common exudative effusions (parapneumonic, malignant and tuberculous) should be stressed.

Parapneumonic effusions due to a nontuberculous bacterial infection are relatively common (40 percent to 50 percent).[1] Whereas most parapneumonic effusions clear spontaneously without the use of chest tubes[2,3] the treatment of each patient should be individually determined. The features that would favor chest tube drainage include the following: (1) increasing effusion or loculation of fluid despite antibiotic medication; (2) persistent febrile course despite antibiotics, and (3) pleural fluid analyses that reveal gross pus, organisms on Gram stain, a glucose level of less than 40 mg per dl, a serum lactate dehydrogenase level of more than 1,000 mg per dl or a pleural fluid pH of less than 7.00 in the absence of systemic acidosis.

While an exudative effusion due to direct tumorous invasion of the pleural space may develop in a patient with a primary pulmonary malignancy, the more common basis for such effusions is extension of the tumor to mediastinal lymph nodes with resultant lymphatic obstruction.[4-5] Therefore, the presence of such an effusion often highlights the need for mediastinal lymph node exploration (mediastinoscopy on the right side and anterior thoracostomy on the left). In the absence of evidence of tumor extension on pleural fluid analysis (cell block) or pleural biopsy, the resectability status of many of these tumors depends on the results of such mediastinal lymph node exploration.

Tuberculosis is a common cause of an exudative effusion. While the pleural fluid may be positive on smear for *Mycobacterium tuberculosis* (usually

less than 25 percent of patients), this diagnosis depends on the triad of histologic examination of a pleural biopsy, culture of the pleural tissue obtained by pleural biopsy and pleural fluid cultures for tuberculosis.[6] The diagnostic yield is increased if each of the components of this triad is done because although approximately two thirds of each can be positive in a group of patients with tuberculosis, in an individual patient only one of these examinations may be positive.

Finally, a management problem should be stressed. If a thoracentesis is carried out, and a considerable amount of fluid is withdrawn (250 to 1,000 ml), a patient may have a fall in arterial oxygen tension, that is, an intrapulmonary right to left shunt may be produced.[7] The physiologic mechanism for such a shunt is that the withdrawal of the pleural fluid may result in re-perfusion of an atelectatic lung zone in the absence of restoration of ventilation to that lung zone. Such patients should be followed with sequential analysis of arterial blood gases, and they should receive supplemental inspired oxygen, if necessary.

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Tobacco and Cancer

THE SURGEON GENERAL is mandated by Congress to prepare an annual report on the health consequences of smoking. These reports have contributed to public understanding of the health hazards of smoking and to the steady decline in the proportion of adult cigarette smokers in the United States. The 1982 Report of the Surgeon General[1] is the first to focus solely on the relationship between tobacco and cancer. Its conclusions are sobering.

In spite of recent, dramatic improvements in the diagnosis and treatment of certain forms of cancer, the overall cancer death rate in the United States has increased. Tobacco-related forms of cancer are responsible for this increase, with lung cancer, alone, accounting for 25 percent of all cancer deaths. Smoking is responsible for the majority of deaths due to cancer of the lung, larynx, oral cavity and esophagus; it is a contributing factor in the development of pancreatic, renal and bladder cancer. A possible relationship between smoking and cancer of the uterine cervix and gastric cancer is also cited. Overall, in the United States in 1982 an estimated 130,000 deaths, or 30 percent of all deaths from cancer, are attributable to smoking. This grim picture is explained, in part, by the poor prognosis of tobacco-related cancer; for example, the five-year survival rates for cancer of the lung, esophagus and pancreas are approximately 10 percent, 3 percent and 1 percent, respectively. The overall cancer mortality rate for male cigarette smokers is increased twofold, but it may be increased threefold for heavy smokers compared with nonsmokers. The risk for cancer of the oral cavity, larynx and esophagus is approximately the same among smokers of cigarettes, pipes and cigars.

In the 1982 Report, evidence is cited concerning the development of cancer at sites not directly exposed to tobacco smoke, such as the pancreas, kidney and bladder. Several organ-specific carcinogens present in cigarette smoke are listed. The consumption of "smokeless tobacco" has increased, and the 1982 Report cautions that popular snuff tobaccos contain "the highest levels of carcinogenic nitrosamines reported in a consumer product that is taken into the body." Studies indicate that nicotine may be an important cocarcinogen. Tobacco additives are identified as substances that should receive closer scientific scrutiny. Concern is also expressed about the possible transplacental carcinogenic effects of tobacco smoke constituents.

Sidestream smoke, which is emitted from the burning cone between puffs, contains carcinogens that are inhaled by both smokers and nonsmokers. There is no known safe threshold of exposure for these substances. In recent studies from Greece and Japan, nonsmoking wives of cigarette smoking husbands were found to have an increased risk for the development of lung cancer. Although these are preliminary findings, the prudent approach is to avoid secondhand tobacco smoke exposure whenever possible.

The 1982 Report provides a final optimistic note:

smoking prevalence among both adult and adolescent cigarette smokers in the United States is declining. Furthermore, new preventive research strategies for teenagers, which stress recognizing and dealing with peer pressures, have resulted in as much as a 50 percent reduction in beginning-smoking rates.

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The AMA and a National Health Policy

A RECENT ANNOUNCEMENT by the American Medical Association that it proposes to assume leadership in the development of a national health policy primarily within the private sector could signal a watershed in the national approach to dealing with the compounding problems the nation faces in health care. That task will not be easy. Policymakers and institutions in both the public and private sectors have long been active in this field, yet no generally acceptable, workable national health policy for the long term has yet emerged.

The timing for such a new approach seems particularly auspicious. Americans seem more focused on health and its enhancement now than at any time in their history. For some decades we have been spending more and more for health and health care until now nearly 10 percent of the gross national product is spent for these purposes. Patient care in the United States is generally conceded to be the best in the world. And, significantly, as a nation we seem for the time being at least to have rejected centralized, nationalized, government controlled health care. But all is not well. There is an obvious need for a long-term national health policy that is acceptable and workable, and right now there is a relative vacuum of effective leadership in this field. The opportunity should be seized. The time may come when the nation may have another, perhaps grander, objective than health.

It is noteworthy that this health care system has long since passed the point where doctors, hospitals or any other single segment of it (and this includes government) can ever hope to control it without the help and cooperation of the other segments. There are some who still believe that government could of course do so, but the evidence to date is that this is not likely to be the case. So far unilateral government initiatives in health care have fallen far short of what needs to be done and generally seem to have caused more problems than they have solved. Could it be that the health care enterprise is developing into something of a new phenomenon in America—or anywhere else for that matter? Could it be that for the first time we are starting to see the massive fiscal and human dimensions of what can occur when new science and expensive technology are rather quickly developed and put to widespread human use, and the intricate professional, technologic, social, economic and political interdependencies that ensue? For many reasons this seems to be a truly new phenomenon, which has surfaced first in the health field, but is no doubt destined to turn up in other fields as well, when comparable conditions develop.

For nearly 40 years the nation has given special attention and special support from both public and private sources to biomedical research, to health professional education and to making the benefits of rapidly accumulating new knowledge and new technology readily available to as many people as possible. As a result a new kind of system of interdependencies has come into being that is as yet poorly understood and certainly does not behave according to the rules for simpler systems. As has been said, if you push the health care system in one place it just bulges somewhere else. It is suggested that this new kind of system is one of interdependencies among relatively independent and autonomous parts. This in turn suggests that if there is to be policy and direction, it will need to be developed internally within the system with involvement and consensus among all or most of the essential autonomous and independent, yet interdependent, parts.

The AMA is to be commended for its proposed approach to developing a national health policy. It plans to involve "such organizations as specialty societies, the American Hospital Association, Blue Cross-Blue Shield, the American Dental Association, the American Nurses Association, the National Medical Association, The Health Insurance Association of America, representatives of the business community such as Chambers of Commerce and The Business Round Table, representa-

tives of labor and other organizations and groups." This is clearly a step in the right direction. But for it to succeed it is essential that no significant segment of the health care enterprise be left out of the policy making process. If a national health policy is to be agreed to, refined and implemented over time, all of the essential but relatively independent and autonomous parts should be party to the decisions on policy as well as responsible for their part in the implementation of it. A notable omission from a list published by the AMA of proposed participants is government. Almost all would agree that government is an important, indeed essential, segment of the interdependent health care enterprise. This and perhaps other omissions could turn out to be fatal flaws in what otherwise could prove to be a brilliant conception.

—MSMW

Some Economic and Human Aspects of Cost Control in Patient Care

IF ANY FURTHER PROOF were needed that purely economic considerations have profoundly altered the relationship between physicians and their patients and the public at large, that proof will be found in the Omnibus Budget Reconciliation Act of 1981 (PL 97-35). Prompted by the "runaway costs" of Medicare and Medicaid, the Budget Act marks the beginning of the federal government's new policies regarding medical care. The emerging policies have at least two main purposes: to restrict the role of government in medical care and decrease the amount of regulation (the good news), but also to reduce, abruptly and sharply, the federal subsidy of care for the elderly and the poor (the bad news for millions of patients).

This focuses attention on a need to increase the effectiveness of the Voluntary Effort by finding ways to avoid ordering unnecessary tests, procedures and drugs. This is a maxim that long antedates the term "cost containment," but there has been lack of guidance on just how to devise a method that will fit individual circumstances. Now McPhee, Myers and Schroeder, elsewhere in this issue of the journal, have provided us an annotated bibliography that will lead us to answers for five key questions: Just how serious is this problem? Do excessive testing and prescribing have other than financial risks for patients? How do you decide rationally whether or not a special test is worth ordering for a particular patient? What are some of the methods of educating house staff and other physicians about these matters? What are the results of these efforts?

This excellent bibliography is really a program of self-directed continuing medical education (CME) for physicians. Reading the most pertinent references will reward those who do this with the information and techniques that will help to make the ordering of tests and the prescribing of drugs as rational as the present state of medical knowledge permits. Also, it can be confidently predicted that decision analysis in its various forms will increasingly permeate the literature and formal CME courses.

The reason for the importance of this is simply that cost containment, along with accountability, will be the major issue of the 1980's. Profound as its immediate effects will be, the Budget Act of 1981 is only a stopgap measure. After it will come longer range approaches to restraining the current rate of increase in Medicaid and Medicare expenditures specifically and in total health expenditures generally (which are now close to 300 billion dollars a year). The most widely promoted "solution" is reliance on the "market forces" that will be unleashed by "competition." Although this is an idea whose political time has come, the belief that the "market approach" will control the rate of inflation in medical care costs is largely a theoretical deduction from untested and probably untestable economic assumptions.

Several legislative proposals that apply this rationale are now before the Congress. In varying combinations and degrees these propose to implement the competitive approach by changing the incentives for consumers (patients) by increasing deductibles and copayments, educating the public to the reasons for the high costs of medical care and encouraging patients to shop around for quality care at the price they are willing to pay. The underlying premise is that once the consumers' (patients') behavior is altered, providers (physicians and hospitals) will be forced to compete by developing highly efficient alternative delivery systems.

The Reagan administration looks upon health maintenance organizations (HMO's) as one of the viable alternative systems. Present evidence indicates that greater economic efficiency is found only in unique HMO's (like the Kaiser model, which

is not an HMO at all) or in HMO's in unique settings (like those in Minneapolis). Whether or not independent practice associations (IPA's) will be able to demonstrate the expected economic benefits of competition is a wide-open question. They will certainly be given all the chance they need to show their superiority to HMO's.

Announcement of the budgetary stringencies was accompanied by the expected homily: "quality of care must not be sacrified to save money." Yet the administration has shown that it looks more to cost-benefit analysis than basic human values in considering how it shall regulate. The US Supreme Court not long ago rejected this approach.[1] The issue was the government's proposal to relax present standards governing the permissible amount of cotton dust in work places and to base new standards on the results of cost-benefit analysis. However, the court decided that the government was required to adopt standards that would assure "to the extent feasible," on the basis of the best available evidence, that no employee shall suffer material impairment of health or functional capacity even if regularly exposed to the hazard throughout the employee's working life. The court held that the original law intended to favor the worker's health above all other considerations, so long as the standard could be achieved technologically and without forcing the industry into bankruptcy.

One of the pressures for rationing medical care through budget restrictions is the steady drum beat of dire predictions by some economists that costs of medical care alone will soon dislocate the entire economy and the public will then rise up in violent protest against the excesses of medicine. But it has yet to be shown that the public really wants a cap on medical expenditures except in the abstract sense. When it comes down to an individual person or a loved one, the answer is obviously different.

The present developments offer American medicine an unusual opportunity to act in behalf of patients' and the public's interests. First of all, each physician can do all that it is reasonable to do in his or her own practice to order only those tests, procedures and drugs that are indicated and known to be helpful in particular situations. The aggregate effect of this on a national scale will be savings of millions of dollars a year. Some of those savings might then be available to pay for care for additional numbers of the elderly and the poor.

The second challenge is to document systematically the "material impairment of health and functional capacity" of patients who no longer receive needed services. The absence of such documentation reinforces the notion, widely held among legislators and public interest groups, that there is enormous waste and unnecessary care in the system. Physicians are in a position to come up with unassailable evidence to the contrary by setting up surveillance programs as extensions of peer review activities that will record the impact of inadequate or insufficient care mandated by the federal cutbacks.

The compilation of such unfortunate events would document in a publicly accountable manner the special efforts practitioners are making to redress the harm that will come to many patients in every community. More practically, such documentation would confront those who make and implement the "tough new fiscal policies" (legislators, elected officials and appointed administrators) with the human consequences—pain, suffering and disability—of what would otherwise be perceived as merely prudent financial restraint.

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Don't Kid Around

EVERY YEAR 1,200 CHILDREN under the age of five are killed while riding in automobiles. More than 60,000 are seriously injured. The best estimates predict that most of these deaths and injuries, perhaps as many as 85 percent, could have been prevented if all child passengers had been restrained properly. If physicians had an equally effective vaccine that could be injected in the office, it would be given. So far, however, few hospitals or physicians have bothered to give even information about restraints for child passengers.

Appropriate restraints are readily available. The types crash-tested and approved by the National Highway Traffic Safety Administration cost as little as $35 and as much as $70. Because child passenger deaths and injuries are the most common cause of death during early childhood, these restraints are logically a priority for preventive education by the medical profession. We cannot inoculate against child passenger injuries; we must educate. This education, it seems, is best given in

prenatal classes. These programs affect a large number of expectant parents, and information on child car-safety given before birth seems to be more effective (in terms of parent compliance) than the same information given at any other time. Therefore, hospitals that have obstetrics programs should —and must—become interested. But the sad facts are, as Dr. Chang and Ms. Levy point out elsewhere in this issue, that fewer than a third of the hospitals in California providing childbirth education include information on infant car-safety, and that information is usually rudimentary.

Dr. Chang and Ms. Levy have determined that 70 percent of hospitals they surveyed are interested in developing more comprehensive programs in child passenger safety, which is gratifying to the three organizations that have been its major proponents: the American Academy of Pediatrics, the National Safety Council and the American Trauma Society. Reports show that fewer than 25 percent of infants are safely restrained when they take their first ride—home from the hospital —and some of us feel the figure may be as low as 10 percent. Each of the above organizations keeps useful information on the availability of child car-safety education for those who provide perinatal services. Each has educational materials and curricula available for use by hospitals and pediatricians, such as the American Trauma Society's program, "Don't Kid Around." Information on how to shop for and use effective child passenger restraints is available from all of them.

The benefits of such prenatal child car-safety programs are no pipe dream. Tennessee, the first state to pass a forceful law requiring the use of child passenger restraints, has achieved an unprecedented and dramatic drop in child fatalities in the few years since the law's passage. Ten other states have followed suit. California has a weak law (giving police officers the authority to issue a verbal warning to the driver of a car carrying unrestrained children) that we expect will have little effect on the death rate of children. Senate Bill 537, currently under consideration by the California legislature, would be more effective, but its chances of passing this session are not good. Meanwhile, dispensation of information to the parents by doctors, childbirth educators or hospitals is all we have to rely on.

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On Having Encounters With Patients

A NEW WORD is creeping into the lexicon of patient care. In the jargons of medical sociology, medical economics and sometimes even of public health the word *encounter* is beginning to be used to describe the professional happening that occurs between a patient and a doctor or other health professional. One senses another step in the semantic degradation of the doctor-patient relationship. In this new jargon physicians and other health professionals are already referred to as *providers* and patients are increasingly called *consumers*. These words are gaining wider use and sometimes even find their way into such hallowed journals as this. An encounter, then, is a new description for what happens when a health care provider and a consumer of health care interact professionally in patient care delivery.

The term seems unfortunate. *Webster's New Collegiate Dictionary* defines encounter as "a meeting between hostile factions or persons," or "a chance meeting" or "a direct often momentary meeting." None of these definitions seems to do justice to the often very personal and it is to be hoped always truly collaborative event that takes place in a meaningful doctor-patient relationship. The word encounter somehow doesn't fit. Its increasing usage in this context seems wrong. But language is made up of the words people use and the ways they use them, and it now seems inevitable that more and more physicians are going to have more and more encounters with their patients—irrespective of whether we like or ever use the world.

—MSMW

CASE REPORTS

Refer to: Meshkinpour H, Vaziri ND: Association of myoglobinuria with adenovirus infection. West J Med 1982 Aug; 137:130-132

Association of Myoglobinuria With Adenovirus Infection

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NONTRAUMATIC RHABDOMYOLYSIS and myoglobinuria associated with a variety of toxic, ischemic, metabolic and inflammatory disorders have been reported with increasing frequency in recent years. The reported association of myoglobinuria and rhabdomyolysis with infectious agents, however, has been limited. Sporadic cases of myoglobinuria have been reported with influenza,[1-7] Coxsackie,[8] herpes simplex[9] and Epstein-Barr[10] viral infections. We describe herein the occurrence of severe myoglobinuria and rhabdomyolysis in a patient with adenovirus infection.

Report of a Case

A 20-year-old man was seen with a two-day history of fever, nonproductive cough, generalized muscle ache, weakness, malaise and the passage of dark brown urine. He had not consumed alcohol or drugs, nor had he engaged in strenuous activities before his illness. He was in excellent health before this episode and his personal and family histories revealed no evidence of muscular disorders or other major medical problems. On physical examination the patient appeared well nourished and well developed. His pulse rate was 86 per minute, blood pressure 120/80 mm of mercury and rectal temperature 38°C. The pharynx was congested but no exudate was seen. His muscles, though normal in shape and strength, were moderately tender to palpation, particularly in the back, lumbar region and thighs. The physical findings were otherwise unremarkable.

Initial laboratory studies showed hemoglobin of 17.3 grams per dl, hematocrit of 49.9 percent and 7,200 leukocytes per cu mm with a normal differential. His serum was clear but his urine was dark brown and showed a strongly positive reaction on benzidine test. Mild proteinuria was noted and there were 0 to 2 erythrocytes and a similar number of leukocytes per high-power field. Other laboratory studies gave the following values: serum sodium 138, potassium 4.1, chloride 102 and bicarbonate 26 mEq per liter; blood urea nitrogen (BUN) was 25 mg per dl, serum creatinine 1.1 mg per dl, serum aspartate aminotransferase (formerly, glutamic-oxaloacetic transaminase, SGOT) 3,780 IU per liter (normal, 8 to 50), serum creatine phosphokinase (CPK) 133,000 IU per liter (normal, up to 150), serum total bilirubin 0.5 mg per dl, serum calcium 9.3 mg per dl, inorganic phosphorus 3.0 mg per dl and uric acid 8.3 mg per dl. A test for hepatitis B surface antigen and a Monospot slide test for infectious mononucleosis were both negative.

The patient was placed on a regimen of complete bed rest with increased fluid intake and sodium bicarbonate and acetaminophen to be taken orally. During the ensuing ten days the patient's muscle pain and tenderness gradually subsided and the color of his urine returned to normal. Urine output, serum electrolytes, BUN and creatinine remained within normal limits throughout the period of observation. SGOT and CPK levels returned to normal in ten days.

A repeat comprehensive evaluation 14 months later showed entirely normal findings on physical examination, plasma chemistry studies including muscle enzyme, renal function studies and urine analysis.

Serial blood specimens were obtained on days 3, 10 and 17 for serologic studies intended to identify a possible viral cause. Complement fixation tests were carried out on sera taken during the acute and convalescent phases for influenzae

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TABLE 1.—*Complement-Fixing Antibody Titers Determined on Sera Obtained During Acute and Convalescent Periods*

Tests For	Specimens		
	Day 3	Day 10	Day 17
Influenza A	1:8	1:8	1:8
Influenza B	<1:8	<1:8	<1:8
Mycoplasma	<1:8	<1:8	<1:8
Adenovirus	<1:4	1:16	1:32
Coxsackievirus			
B1	<1:8	<1:8	<1:8
B2	<1:8	<1:8	<1:8
B3	<1:8	<1:8	<1:8
B4	<1:8	<1:8	<1:8
B5	<1:8	<1:8	<1:8
B6	<1:8	<1:8	<1:8

A and B, coxsackievirus B1 to B6, adenovirus group and *Mycoplasma*. The results of these studies are shown in Table 1. There was a steady rise in complement-fixing antibody titer against the common adenovirus antigen, suggesting an active infection with this virus. There was no change in the antibody titers against other tested infectious agents.

Discussion

This patient presented with severe myalgia, generalized muscle tenderness, the passage of dark brown urine strongly reactive to the benzidine test in the absence of hematuria, colorless serum and greatly elevated muscle enzyme values. The constellation of these clinical and laboratory findings is characteristic of acute rhabdomyolysis and myoglobinuria.

Strenuous exercise, exposure to various toxins, consumption of alcohol or certain drugs, hyperpyrexia, hypophosphatemia, hypokalemia, acidosis, various genetic enzyme deficiencies and a number of other factors known to predispose to rhabdomyolysis[11-19] were absent in this case.

The presence of a mild to moderate fever, exudate-free pharyngitis, nonproductive cough and normal leukocyte and differential counts suggested a viral syndrome. A greater than eightfold rise (from less than 1:4 to 1:32) in complement-fixing antibody titer[20] against the common antigen for adenovirus is diagnostic of adenovirus infection in our patient (Table 1). Association of rhabdomyolysis with various viral infections including those caused by influenza A, coxsackievirus, herpes simplex, and Epstein-Barr viruses has been reported in recent years.[1-10] The development of severe myoglobinuria and rhabdomyolysis during the acute phase of adenovirus infection in our case suggests a possible pathogenetic relationship. A diagnosis of adenovirus infection could have been easily missed and the illness could have been dismissed as a flu syndrome had we not obtained appropriate serologic tests. Careful investigation in patients with viral syndrome and myoglobinuria may show similar findings in the future. The passage of dark brown urine and profound muscle tenderness occurring during the acute phase of the disease were prominent features of myoglobinuria and rhabdomyolysis in our patient. Similar observations have been reported in association with influenza A infections in adults.[1-6]

One of the major complications of myoglobinuria and rhabdomyolysis is acute renal failure. Renal function remained grossly intact despite severe myoglobinuria in our patient. This may have been partly due to the prompt institution of bed rest, fluid therapy and alkalinization of urine with sodium bicarbonate. Pronounced hyperkalemia, hyperuricemia and hyperphosphatemia are known to occur in acute renal failure associated with rhabdomyolysis. This is due to increased release and reduced excretion of the respective substances in this setting. In our patient, however, none of these features were present. This is probably due to the preservation of his renal function, enabling adequate excretion and preventing a rise in the plasma concentration of potassium, uric acid and phosphorus.

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Refer to: Chan MKL, Hendrickson CS, Taylor KE: Polyarthritis associated with breast carcinoma. West J Med 1982 Aug; 137:132-133

Polyarthritis Associated With Breast Carcinoma

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POLYARTHRITIS HAS BEEN REPORTED to be associated with various types of carcinoma.[1-9] When the primary tumor tissues were removed, the arthritis resolved. Arthritis associated with breast carcinoma was mentioned by MacKenzie and Scherbel,[3] who did not, however, describe the nature and extent of the arthritis. Recently, monarthritis caused by metastatic breast carcinoma was reported by Moutsopoulos and co-workers.[7] We report the case of a patient with breast carcinoma associated with polyarthritis and acute inflammation of the synovial fluid. When the primary tumor was removed, the arthritis resolved within a week.

Report of a Case

A 44-year-old East Indian woman without a history of arthritis was admitted to hospital with a temperature of 37.9°C (100.2°F), malaise and severe incapacitating pain at the right hip and both knees and ankles for three days. A week before the onset of arthritis, she had a needle biopsy of a breast nodule.

At the time she was admitted to hospital, findings on physical examination included a sinus tachycardia of 120 beats per minute with a grade 1 of 6 systolic ejection murmur and a 1.5-cm firm, mobile nodule in the left breast. Tenderness and pain with range of motion were elicited at the right hip. Active synovitis with pain, tenderness, warmth, erythema and moderate swelling was observed at both knees and ankles. Laboratory findings were as follows: a leukocyte count of 11,300 per cu mm with no left shift, a hematocrit of 38 percent and an erythrocyte sedimentation rate (Westergren method) of 90 mm per hr (repeat testing showed 148 mm per hr). The results of electrolyte, liver function, rheumatoid factor and antinuclear antibody (ANA) tests were all normal. Analysis of knee aspirate gave the following values: leukocyte count, 65,000 per cu mm, with 94 percent polymorphonuclear leukocytes; glucose, 111 mg per dl; protein, 5 grams per dl; C_3, 81 mg per dl; no crystals; negative findings on acid-fast smear, and negative cultures for *Neisseria gonorrhoeae* and *Brucella* sp. Cultures of specimens from throat and cervix showed normal flora; the results of blood cultures were negative. The patient was given penicillin and nafcillin intravenously but continued to have temperatures up to 39.6°C (103.3°F) with nausea and vomiting. No apparent improvement occurred in her joint symptoms, and antibiotic therapy was discontinued. The fever abated, however, and she was discharged on a regimen of indomethacin.

The joint symptoms lessened slightly during the next few weeks, then recurred. Active synovitis with symmetric distribution now affected the proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, knees and ankles. X-ray films of the sacroiliac joint and hips were normal. She was treated with naproxen and given an intramuscular injection of dexamethasone; her condition improved moderately. The biopsy specimen of the breast nodule showed medullary carcinoma, for which mastectomy was carried out. No lymph node involvement was found. Naproxen therapy was discontinued postoperatively. Three days after the operation, her joint symptoms de-

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creased considerably; by the seventh postoperative day, all joint symptoms had resolved. At multiple follow-up visits over the next 12 months, the patient showed no evidence of arthritis.

Discussion

Various musculoskeletal symptoms have been described as the presenting features of an underlying malignant condition. These symptoms, ranging from myalgia and arthralgia to clinically evident monarthritis or polyarthritis, all resolve when the primary tumor is removed. In our patient, a rapid and disabling polyarthritis developed, which was only partially controlled with nonsteroidal antiinflammatory drugs. When a breast tumor was removed, the arthritis resolved within a week.

The data in the literature on synovial fluid analysis in patients with a malignant lesion have been sparse. Noninflammatory fluid has been described by Ropes and Bauer[10] in patients with pulmonary hypertrophic osteoarthropathy and in the patients reported by Moutsopoulos and associates.[7] In our patient, analysis of a specimen of the synovial fluid from the knee showed an acute inflammatory reaction. Zacharski and Kyle[11] reported that the erythrocyte sedimentation rate was greatly elevated (more than 100 mm an hour, Westergren method) in patients with malignancy. In our patient, the erythrocyte sedimentation rate was elevated to 148 mm per hour (Westergren method).

The pathogenesis of arthritis in association with malignancy is unknown. Husain and colleagues[12] showed a positive result on ANA test to be associated with carcinoma. Sheon and associates[13] reported a positive rheumatoid factor in 27 percent of patients with malignancy. In Bartfeld's[14] survey the incidence of positive rheumatoid factor in patients with malignancy ranged from 1 percent to 20 percent. Circulating immune complexes and hypocomplementemia in patients with carcinoma were reported by Teshima and co-workers[15] and by Rosen and colleagues.[16] Recently, the prostaglandin E_2 (PGE_2) level was shown to increase in patients with metastatic bone disease.[17,18] Pretreatment with administration of indomethacin reduces the amount of PGE_2 extractable from the tumor, as has been proved by Galasko[19] and by Voelkel and associates.[20] Bennett and co-workers[21] and Easty and Easty[22] separately found an increased level of PGE_2 in breast carcinoma tissues. This finding was recently confirmed by Rolland and colleagues.[23] Prostaglandin E_2 is known to be one of the mediators of inflammation. Whether this local increase in PGE_2 relates causally or temporally to the development of arthritis needs further investigation.

Summary

Polyarthritis associated with several types of carcinoma has been reported. We report the case of a patient with breast carcinoma in whom polyarthritis resolved when the tumor was removed. An increase of the amount of prostaglandin E_2 in breast carcinoma tissue, which has been reported in the literature, might be related to the development of arthritis.

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Metaldehyde Poisoning From Slug Bait Ingestion

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WE RECENTLY CARED FOR a patient with massive metaldehyde poisoning and report the case to familiarize physicians with the toxic effects of the substance, as well as to outline a rational approach to future cases.

Report of a Case

A 32-year-old woman, a grade school teacher, had a one-year history of depression and several suicide attempts. Early one morning she swallowed approximately 470 ml (16 oz) of a commercial liquid slug bait (Deadline, Pace National Corporation) that contains 4 percent metaldehyde; in all, 18.9 grams or approximately 330 mg per kg of body weight was ingested. All other ingredients are inert without known toxicity.

She soon had nausea and then vomiting. Two hours after the ingestion she had the first of many generalized convulsions. Initially she was treated at a local hospital with gastric lavage, activated charcoal and diazepam, but later that day was transferred to Harborview Medical Center (Seattle) because of continuing convulsions, decreased mental status and muscle spasms. By the time transfer was completed the patient was comatose.

On examination she was found to weigh 58 kg, her blood pressure was 130/90 mm of mercury, temperature 38.1°C and respirations 20 per minute. An endotracheal tube was in place. Findings on general examination were unremarkable except for healed lacerations on her wrists and neck. On neurologic examination she was noted to be unresponsive to voice or painful stimuli. Pupils were reactive, eye movements were full on horizontal oculocephalic reflexes and corneal reflexes were present. Tone and tendon reflexes were diffusely increased though there were flexor plantar responses. Chvostek's sign was present. Laboratory testing was remarkable for an unmeasured anion gap of 23 mEq per liter, though the arterial blood gas determinations showed respiratory alkalosis with pH 7.57 and carbon dioxide partial pressure (Pco_2) 21 mm of mercury. Urine pH was 5.5 with ketones present. Serum calcium and magnesium levels were normal. Toxicologic studies on blood and gastric contents were negative except for an unidentified substance.

Her hospital course was complicated by severe muscle spasms and repeated generalized convulsions despite therapeutic concentrations of phenytoin and phenobarbital in the blood. Diazepam administered intravenously only briefly controlled the spasms and convulsions. Although the serum creatine kinase level was elevated to four times normal, significant myoglobinuria did not develop. She also had pneumonia, increased oral and tracheobronchial secretions and elevated serum transaminase levels, which peaked during the second week and returned to normal by the time of discharge. Convulsions continued for three days, during which time an interictal electroencephalogram showed diffuse slowing with scattered epileptiform discharges. The coma lasted for seven days but tracheal intubation was prolonged to nine days due to general weakness and excessive secretions.

When communication became possible the patient was noted to have pronounced memory deficits, an exaggerated glabellar reflex and prominent snout and palmomental reflexes. Three months before this admission, the findings of a detailed neurologic examination (done during a hospital stay for a suicide attempt) had been entirely normal.

Her strength improved and administration of anticonvulsant drugs was discontinued. Findings on lumbar puncture and contrast-enhanced cranial computerized tomography were normal. Although her mental status improved slowly, at best she had a poor recent and remote memory, flat affect and pronounced latency of response. She was subsequently transferred to the psychiatric service. A repeat electroencephalogram was normal. Psychological testing showed a verbal intelligence quotient (IQ) of 100 and a performance IQ of 88 with a full scale IQ of 94; Halstan-Reitan battery impairment index was 0.7. Primarily she had an

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adaptive problem-solving impairment and severe impairment of memory in both verbal and visual-spatial areas. The patient was discharged 51 days after the attempted suicide.

One year after the poisoning, the patient reported by telephone that her memory had returned almost to normal. Although still unemployed, she had plans to eventually return to teaching. She declined a more formal follow-up evaluation.

Discussion

The first cases of metaldehyde poisoning occurred in the 1920's when metaldehyde was used as a combustible, that is, "meta-fuel" tablets.[1-3] The cases reported from Great Britain and continental Europe were similar to the present case, with vomiting, convulsions and coma being prominent features. It was not until the 1930's that by serendipity metaldehyde was discovered to be a potent molluscicide: "A lady who was using 'meta-fuel' to heat her curling tongs and threw the remains out the window afterwards observed an assemblage of dead slugs."[4]

There have been few reports of serious metaldehyde poisoning with slug or snail baits in humans,[5-6] and serious accidental poisonings with the meta-fuel tablets have been reduced since the introduction in 1932 of a peppery coating on the tablets. Intentional poisoning with the tablets has continued mostly with suicide attempts, though homicides have been reported as well.[3]

Borbely[7] has reviewed 213 cases of metaldehyde poisoning gleaned from the 15,000 cases in the Swiss Toxicological Information Center between 1966 and 1969. All the cases of poisoning in children were accidental and were divided equally between meta-fuel tablets and molluscicides. In adults 20 of 24 cases were intentional and all involved the tablets. As would be expected with the higher concentration of metaldehyde in the tablets, most of the cases with severe symptoms involved tablets and only one involved a molluscicide. In most children there were minimal symptoms and none died. Both fatalities in the series had intentionally taken a large number of the tablets. Although complete information was not available in all cases, Borbely was able to establish a relationship between amount of metaldehyde ingested and subsequent symptoms, as shown in Table 1.[7]

Long-term sequelae from serious poisonings are not well described. Our patient's memory problems that improved with time are of interest.

TABLE 1.—*Metaldehyde Poisoning: Relation Between Ingested Dose and Clinical Effects**

Dose	*Clinical Effects*
Traces (a few mg/kg)	Salivation, facial flushing, fever, abdominal cramps, nausea, vomiting
Up to 50 mg/kg	Drowsiness, tachycardia, spasms, irritability, salivation, abdominal cramps, facial flushing, nausea
50-100 mg/kg	Ataxia, increased muscle tone
100-150 mg/kg	Convulsions, tremor, hyperreflexia
150-200 mg/kg	Muscle twitching
Approximately 400 mg/kg	Coma, death

*Adapted from Borbely.[7]

Ludin[3] reviews the report of a person who intentionally ingested approximately 2 grams of metaldehyde to see if it had the same hypnotic effect as paraldehyde. The acute symptoms were as described in the first two categories in the table but he also reported a prolonged (weeks) yet reversible memory loss.

The frequency of poisoning in the United States is unknown. From 1966 to 1980 the Environmental Protection Agency (EPA) Pesticide and Toxic Substance Branch found that 76 of 34,616 incidents reported involved metaldehyde, mostly in molluscicides, meta-fuel tablets not being available in the United States.[8] There were 52 cases of metaldehyde poisoning in humans and 40 of 44 home exposures involved children. Among the children, symptoms were minimal or absent and there were no deaths. In three cases, including the one reported here, the poisoning was severe. In one, nausea, vomiting and coma occurred without other known details. In another, a 36-year-old man ingested metaldehyde in an ethylene glycol base. Vomiting, acidosis, tremulousness, convulsions and coma ensued. The course was stormy but not fatal. None of the exposures in humans reported by the EPA is known to have resulted in death.[8]

Of the approximately 187,000 cases reported to the National Poison Center Network in 1979 from all regions of the United States, 25 involved metaldehyde.[9] All 25 were children, 24 of whom were treated at home, only one being seen in an emergency room. In all, 21 of the 25 were asymptomatic, 4 had mild symptoms and none died. Interestingly, 80 percent of the reports came from Washington State. Unfortunately the reports to

the center are not complete and cases from Oregon and California are not included. Given the density of slugs and snails—and hence molluscicide use—on the West Coast, exposures are probably high throughout this area.[10] Most of the cases reported by the EPA came from California. Drs. K. Mattie and A. Peoples, Worker Health and Safety Bureau of Pest Management, State Department of Food and Agriculture, have monitored metaldehyde poisoning in California and also report that ingestion is common, almost always in children and almost always asymptomatic (oral communication, January 1981).

How metaldehyde produces its toxic effects is unknown. Like paraldehyde it is a cyclic polymer of acetaldehyde, to which it may decompose in the body.[10-12] Evidence for such a breakdown is minimal, though in two dogs with fatal metaldehyde poisoning acetaldehyde was found in the stomach contents,[13] and it is known to depolymerize readily in an acid medium. The toxic effects of metaldehyde could be produced directly, through intermediate breakdown products or through acetaldehyde, which is readily absorbed from the gastrointestinal tract.[14]

Although little is known about metaldehyde or its intermediate breakdown products, a great deal is known about acetaldehyde because of its suspected role in the toxicity of ethanol. The effects of metaldehyde poisoning (see Table 1) are similar to those seen with disulfiram (Antabuse) reactions, which are presumed due in part to increased acetaldehyde.[15] Convulsions have been described with severe reactions, especially in animals.[16]

The toxic effects of acetaldehyde have been the subject of extensive study.[14,17,18] Central nervous system toxicity may be mediated through competition between acetaldehyde and biogenic aldehydes (breakdown products of the biogenic amines) for aldehyde dehydrogenase with inhibition of oxidative pathways. Dopamine and serotonin would be affected more than norepinephrine, which relies more on aldehyde reductase. The effects of the biogenic aldehydes are unknown, though they may be important in alterations of consciousness during sleep.[19] Biogenic aldehydes can also undergo condensation reactions with other biogenic amines and aldehydes to produce alkaloids, similar to the process in poppies that leads to the formation of the alkaloid morphine. Such reactions are augmented by acetaldehyde, which itself can condense with dopamine to form salsolinol, an alkaloid shown to affect brain calcium metabolism and to be reversed by naloxone hydrochloride.[20] Whereas acetaldehyde competitively inhibits the aldehyde dehydrogenase pathway, the alternate aldehyde reductase pathway for breakdown is inhibited by barbiturates and phenytoin.[19] In the treatment of convulsions in metaldehyde poisoning, therefore, not only is paraldehyde—a congener of metaldehyde—probably contraindicated, but so may be phenobarbital and phenytoin. In our case high doses of the latter drugs failed to control the patient's convulsions.

Unfortunately neither acetaldehyde nor metaldehyde levels were measured in our case. Assays for these substances are not readily available. Another way to monitor someone with known metaldehyde poisoning might be to measure ethanol levels, since ethanol would be formed from the acetaldehyde by the reverse alcohol dehydrogenase-catalyzed reaction.[17]

The mixed metabolic and respiratory alkalosis is of note. Although lactic acid formed during repeated convulsions may have contributed to the acidosis, metaldehyde itself may have been the cause by mechanisms similar to those described in paraldehyde overdoses.[21] The respiratory alkalosis may have been caused by acetaldehyde formed from metaldehyde. Injecting acetaldehyde intravenously into humans, Asmussen and co-workers[22] found it produced a pronounced increase in minute ventilation.

If one assumes the major toxicity from metaldehyde poisoning to be through acetaldehyde, are there therapeutic implications? Numerous agents including *D*-penicillamine, *N*-acetylcysteine, thiamine and ascorbic acid have been shown in experimental animals to lower blood levels of acetaldehyde given orally or induced by alcohol, that is, disulfiram reactions.[16,17,23,24] Acetaldehyde is thought to condense nonenzymatically with sulfhydryl to form thiazolidine compounds, which are excreted in the urine. Thus the blood levels of acetaldehyde are lowered, and its pharmacologic effects are reversed. Although *N*-acetylcysteine given by mouth is a suggested treatment for acetaminophen poisonings,[25] more data are needed before it can be recommended for metaldehyde poisonings.

This information suggests a rational approach to the treatment of metaldehyde poisoning. Usual measures should be carried out, including gastric lavage with bicarbonate solution to decrease acidic breakdown of metaldehyde to acetaldehyde, in

addition to giving activated charcoal and cathartics. Flushing, nausea, vomiting, increased secretions and decreased mental status should be anticipated and the trachea intubated early when airway protection or controlled ventilation is needed. Convulsions are common and should be treated with diazepam given intravenously. Paraldehyde should be avoided because it is a congener of metaldehyde. Although phenobarbital and phenytoin theoretically may have deleterious effects, convulsions must be controlled. Dialysis is said not to be effective.[7] Finally, if convulsions are uncontrolled and elevated blood acetaldehyde levels can be documented, a trial of *N*-acetylcysteine or *D*-penicillamine should be considered. Although it rarely causes severe poisoning, metaldehyde can be fatal, as reported in the literature, and can be associated with considerable morbidity as in our case.

Summary

Metaldehyde poisoning has a long history in Europe due to ingestion of meta-fuel tablets, a combustible agent. In the United States, however, exposure to metaldehyde occurs with ingestion of molluscicides (slug and snail baits) and serious poisoning has only rarely been recorded. We describe the case of a 32-year-old woman who intentionally ingested a large quantity of liquid slug bait containing approximately 18 grams of metaldehyde. During a stormy two-week course, vomiting, increased salivation, convulsions and coma developed. Recovery was complicated by prolonged memory and psychomotor dysfunction. Metaldehyde may produce its toxic effects through breakdown to acetaldehyde, of which it is a cyclic polymer. Poisoning with this agent may thus be linked with the toxicity of ethanol and disulfiram (Antabuse) reactions.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

How Much Testing Is Needed?

To the Editor: I was intrigued by the repartee between Dr. Robin and other members of the community hospital medical staff in the Clinical Management Conference in Interstitial Lung Disease published in the April 1982 issue.[1]

The problem of how much of a diagnostic workup one should do or how aggressive one should be with therapy in any given patient has perplexed physicians for generations. In terms of historical time we are not too far removed from the days of decision making for bloodletting. I must take issue, however, with Dr. Robin's analysis of the influence of aging on this decision making process. There are two factors that, in my opinion, strongly influence the role of aging in the making of such decisions.

The first is the social issue that the discussants glossed over lightly in their comparison between the patient and a young alcoholic with cirrhosis. Is the 40-year-old cirrhotic man really going to contribute more to society in his remaining years than would the elderly woman? Even without knowing any more about the patient I would doubt it. Given that this woman statistically has less than five years of life remaining, her contribution to children, grandchildren, neighbors and friends may, even probably will, exceed that of the chronically alcoholic patient who will continue to remain a burden on society and family unless he is willing to cease drinking.

Second, it was unfortunate that the elderly woman was compared with a young alcoholic man with cirrhosis. I suspect that the lifespan for both would not be that much different. Thus, in the comparison of these two persons, age should not really have entered into the discussion. A more appropriate comparison would have been a 50-year-old man with a similar lung problem.

Dr. Robin and the staff also raise the issue of the appropriateness of the number and kinds of diagnostic tests that should be done in light of the possibility that effective therapy may not be available or that chosen therapy might not be influenced by the results of the tests or that the tests would not prove to be helpful in a high percentage of patients. I suggest that such an attitude does little for the advancement of our knowledge or understanding of disease in general or interstitial lung disease in particular. In addition, it strikes me as being very appropriate for any patient to know as precisely as possible the true nature of his or her illness and the possibilities for and consequences of therapy. I believe that to treat a disorder empirically, when it is even remotely possible to obtain a better idea of the nature of the problem, is taking a step backward in medical progress. I do not quibble with the rationale of using some intelligent discrimination in the selection of diagnostic tests, but to treat by guesswork when we do not have to is not appropriate and of and by itself can produce its own harmful consequences.

Although I suspect Dr. Robin was deliberately trying to be provocative, I cannot entirely agree with his arguments and feel much more comfortable in joining the camp of those whose opinion was expressed in the editorial by Dr. Crystal.[2]

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Sickling Crises at High Altitudes

To the Editor: Claster and co-workers' study (in the November 1981 issue) concerning the risks of altitude exposure in sickle cell disorders is fascinating.[1] However, the authors do not state conclusions on two aspects of their data. I believe these are important and need emphasis.

Among the patients in their study, the frequency of vasoocclusive nonsplenic crises was 6.5 percent

in homozygous sickle cell disease (SS) and 5.5 percent in SC/S-β-thalassemia disease. The numbers of patients were 26 and 19, respectively. The difference in frequency between the two groups is not statistically significant ($P>0.05$). Yet the authors state that patients with Hb SC and Hb S-β-thalassemia only should arrange in advance for inflight oxygen. They add: "We believe that adult patients with Hb SS do not need supplemental oxygen unless they are among the 6 percent of adult patients with Hb SS and intact spleens." Admittedly, there are fewer instances of splenic crises in SS disease (4.3 percent as compared with 8 percent in other forms), but it is not splenic crises only that we need to or can prevent by supplemental oxygen. The 6.5 percent of patients with Hb SS who do suffer vasoocclusive crises could benefit from inflight oxygen.

The authors also found that whereas 42.9 percent of SS patients in Reno (elevation 4,400 ft) suffered vasoocclusive crises, only 31 percent of SS patients in Lake Tahoe (elevation 6,320 ft) had similar complications. This difference is significant ($P<0.05$). Watson-Williams also noted this in his critique of the paper,[2] but neither he nor the original authors could provide an explanation for this seeming contradiction. In fact, there is no contradiction. Among other things, the sickling process of deoxyHb S is allosterically modified by pH and 2,3-diphosphoglycerate (2,3-DPG). Lowering the pH hastens sickling by decreasing the oxygen affinity of Hb S via the Bohr effect. In contrast, 2,3-DPG has no independent effect on the polymerization of Hb S. Instead it alters pH, which in turn enhances polymerization.[3] It follows, therefore, that if the pH effect of 2,3-DPG is annulled by respiratory alkalosis, which occurs to a greater degree at 6,300 ft than 4,400 ft, it cannot influence polymerization of Hb S. While this phenomenon cannot adequately explain the reduced frequency of crises in patients from Denver when they are exposed to high altitudes,[4] a comparison of the two studies done so far on the subject[1,4] cannot be made since one recorded the frequency of vasoocclusive *events*[1] and the other recorded the number of *patients* who developed similar symptoms.[4] In any event, this is one of the more intriguing findings in Claster and associates' study and deserves future investigation.

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Diagnosis of Testicular Torsion

To the Editor: Two important caveats should be added to Marshall's excellent, though necessarily brief, review of progress in the diagnosis of testicular torsion.[1] One is that use of a Doppler ultrasonic stethoscope must include compression of the ipsilateral spermatic cord with abolition of pulsations to assure that blood flow through the testicular artery and not inflamed scrotal skin is being tested.[2]

Another caution to practitioners would be that pyuria, while unusual, may accompany torsion.[3,4] Increasing numbers of white cells make torsion less and less likely, but there is no specific dividing line, making consideration of all clinical features, appropriate use of noninvasive tests and early exploration necessary for achieving higher testicular salvage rates.

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Holistic Medicine: Advances and Shortcomings

To the Editor: In "Holistic Medicine: Advances and Shortcomings" in the June issue[1] of the journal, Dr. James S. Gordon's definition of holistic medicine reads very well. However, I would point out that he analyses only an incomplete concept of holistic medicine. One of the references in his paper is to Jerome Frank, professor of psychiatry and behavioral sciences at Johns Hopkins. In a later article, Dr. Frank[2] analyses the three divisions of holistic medicine: the exotic, the supernatural and the naturalistic.

Dr. Gordon seems to have omitted the middle aspect, which Dr. Frank defines as

> a variety of phenomena that have been variously termed paranormal, transpersonal, occult and the like. These include healing through prayer as well as phenomena such as mystical experiences, telepathy and precognition. What they have in common is that they are experienced only in altered states of consciousness and seem to occur in levels of reality or orders of existence that differ fundamentally from the everyday reality in which we live most of the time. Thus, they are "supernatural" in the strict dictionary definition of the term.[2]

This is a far cry from biomedical medicine. There is room aplenty in biomedical medicine for the uniqueness of the individual, patient responsibility for health, influence of social and economic factors, and broadening and enriching of medical practice—items italicized by Dr. Gordon. Holistic medicine sounds inspirational to the uncritical ear, but it includes supernatural subsets that are the antithesis of biomedical practice.

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Needle in the Foot

To the Editor: A needle in the foot is a common problem for all physicians in primary and surgical care. Treatment is compounded by the fact that the removal of the foreign object may involve just a few minutes or, sometimes, hours. This is sometimes accomplished in a physician's office, an emergency room or an operating room. At times, this is done under local, regional or general anesthetic.

Most often, a foreign object in the foot is a sewing needle or a pin.[1] Other objects, such as glass, wooden splinters or fragments of tissue may or may not be radiopaque.

Various techniques have been devised to remove such objects. These include, often, blind dissection through the entry wound, needle localization by stereotactic techniques, xeroradiography[2] or tagging hemoclips[3] and using serial x-ray studies.

Our technique is to bring the patient to the fluoroscopy unit, where the wound is appropriately prepped with a povidone-iodine (Betadine) solution. A small 1-cm incision is made over the entry site of the radiopaque object and a small hemostat is used to remove the foreign body. It is understandable that in watching the object under fluoroscopy, one can have difficulty removing it blindly. The object moves significantly when touched with the hemostat, and sensation of touching a solid object is readily transmitted through the hemostat handle. The hemostat is not opened for grasping until the foreign body is touched.

The most efficient use of a fluoroscope can be best achieved by a position that will allow vertical approach to the foreign body. The hemostat is directly parallel to the fluoroscopic beam, thus insuring contact on the first pass by eliminating the X axis. Under fluoroscopic control, both the needle and the hemostat are visualized and the object is usually quickly removed.

The time required for removal is usually well within one minute. Only rarely does it involve significant discomfort to the patient.

It is our recommendation that in patients with radiopaque foreign objects requiring removal, this be done under fluoroscopic control.

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Thrombotic Thrombocytopenic Purpura

To the Editor: The good discussion of thrombotic thrombocytopenic purpura by Kacich and Linker, which appears in the June issue,[1] is incomplete without mentioning that Moschcowitz first reported that disorder in 1925[2] and that since then it has been known as Moschcowitz's disease.

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Refer to: Papadakis MA: Clinical aspects of infectious mononucleosis (Topics in Primary Care Medicine). West J Med 1982 Aug; 137:141-144

Infectious Mononucleosis

MAXINE A. PAPADAKIS, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

INFECTIOUS MONONUCLEOSIS (IM) is an acute febrile illness of late adolescence and early adulthood caused by the Epstein-Barr virus (EBV), a DNA virus of the herpesvirus group. EBV is ubiquitous and, by adulthood, 90 percent to 95 percent of people have demonstrable EBV antibodies. In the United States, half of children aged 5 have had EBV seroconversion and in many the infection is subclinical. A second peak of infection occurs in late adolescence.

IM is a disease of low infectivity. College roommates of patients with IM have no greater frequency of seroconversion than the general susceptible population. The disease is probably spread by intimate oral contact in young adults, but because there is such a high incidence of asymptomatic carriers, only 5 percent to 10 percent of patients with acute illness can give a history of exposure.

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This work was funded by a grant from the Henry J. Kaiser Family Foundation.

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Clinical Presentation

The typical patient with IM is a young adult aged 15 to 25. Most patients have a gradually worsening prodrome of malaise, headache, fatigability, chilliness, feverishness, anorexia, eyelid edema, and (if they are smokers) a dislike for cigarettes. The headache is retroorbital and there may be photophobia. Except for the presence of eyelid puffiness, these early symptoms are nonspecific and usually last several days. A characteristic clinical triad of fever, cervical adenopathy

and sore throat follows; this is observed in 80 percent to 90 percent of cases in young adult patients.

Fever is virtually always present, with the usual temperature range being between 38° and 39.5°C (100° and 103°F). In most cases of IM, the duration of the acute illness is equivalent to the duration of the fever, usually two to three weeks.

Cervical lymphadenopathy becomes prominent during the first week, stabilizes during the second week and then slowly remits, rarely lasting more than a month. Adenopathy of bilateral posterior cervical nodes is most characteristic, with axillary and inguinal adenopathy less common. Occipital nodes are usually normal, a helpful differential feature from rubella, and hilar adenopathy is very rare. The lymphadenopathy is bilateral and painless, and nodes are not red or fluctuant. There is no correlation between the size of the nodes and the duration of the illness.

Sore throat may be the most troublesome feature of IM. It usually begins during the first week and subsides after the second. On examination exudative pharyngitis may be mimicked. A recurrence of sore throat suggests superimposed streptococcal infection. Transient *palatal petechiae* at the junction of the hard and soft palates are noted in a third of patients, typically during the second week.

Splenomegaly is present in about half of patients, often associated with tenderness to palpation. Vigorous repeated palpation should be avoided to prevent splenic rupture. The splenomegaly usually follows the pattern of change in lymph nodes, returning to normal by one month. However, splenomegaly may be persistent for up to six months or, rarely, for years. Hepatomegaly, which is usually asymptomatic, is seen in 10 percent of patients, but more common is first-percussion tenderness over the liver. *Jaundice* is seen in 5 percent of cases and generally has a benign course. Infrequently, hepatitis can be the predominant presentation and is apt to be associated with high fever, unlike other viral hepatitides.

In upwards of 80 percent of patients with IM a *rash* develops when they are given ampicillin, with a nonpruritic macular or macular-papular rash occasionally developing spontaneously. The former does not imply permanent hypersensitivity to ampicillin, nor is it specific for IM, since it can complicate cytomegalovirus (CMV) infection.

Nasal stuffiness, cough, sputum production, chest pain, joint pains, painful lymph nodes, diarrhea, dysuria or severe abdominal pain are not found.

Because IM is a disease mainly of young adults, most patients over 40 have had previous exposure to EBV and are immune to reinfection. Rarely, IM may develop in older patients lacking such immunity. Difficulty in making the diagnosis stems from not considering the disease in this age group, and older patients may have less cervical adenopathy. Serologic studies do not differ from those of infected young adults, but the clinical course may be severe and complicated.

Laboratory Features

The pertinent laboratory abnormalities in IM are hematologic, serologic and hepatic. In the usual clinical presentation, IM can be diagnosed with a heterophil test and complete blood count only.

The hematologic criterion for diagnosis is an increase in mononuclear cells of greater than 50 percent, with the occurrence of at least 10 percent atypical lymphocytes. During the second and third weeks, the elevated lymphocyte count peaks at 12,000 to 20,000 and occasionally may reach 50,000 per cu mm. Some patients have a leukopenia early in the illness.

Mild neutropenia (2,000 to 3,000 per cu mm) and thrombocytopenia (100,000 to 140,000 per cu mm) are common and resolve in a month. The hemoglobin is usually normal, a helpful differentiating feature from lymphoma and leukemia.

The serologic basis for the diagnosis of IM is a positive heterophil test; the Monospot Slide Test for Infectious Mononucleosis (Ortho Diagnostic Systems, Inc., Raritan, N.J.) is one of numerous available rapid tests for heterophil antibodies. If the Monospot test is negative but it is clinically indicated, one should retest in seven to ten days. Approximately 40 percent of patients have a positive test during the first week, increasing to 80 percent by the third week. In 20 percent, the Monospot test continues to be positive a year after the onset of the illness. The Monospot test should never be considered diagnostic in the absence of clinical or hematologic features of IM. Unusual false-positive results on Monospot tests occur in cases of other viral illnesses (especially rubella) or serum sickness and in patients with non-Burkitt's lymphoma with unrelated EBV infection. In a person with persistently negative Monospot findings in whom serologic confirmation of

IM is necessary, one may do a differential heterophil absorption test, or tests specific for EBV antibodies. The lack of any EBV antibodies rules out the disease.

Because liver function is almost always abnormal in IM, this need not be checked in a routine case. Serum transaminases are most commonly elevated to two to three times normal, with mild elevations of serum alkaline phosphatase and serum bilirubin. The changes are greatest during the second week, with gradual decline over the next month.

In rare cases in which hepatitis predominates in the clinical presentation, the enzymes differ from those of hepatitis A or B. There is a dissociation in IM between an elevated serum alkaline phosphatase and a low serum bilirubin, with moderate rises in serum transaminases.

Complications

IM is usually a benign, self-limited illness and complications are rare, occurring in less than 1 percent of patients. Despite the brevity of the acute illness, debility and lethargy may last for two to three months.

Splenic rupture is a life-threatening complication and occurs in 0.2 percent of cases. As abdominal pain is distinctly unusual in IM, its presence should alert a physician to the possibility of splenic rupture. It is a misconception that IM may mimic acute appendicitis from mesenteric adenitis. Splenic rupture can occur spontaneously, as well as after abdominal trauma. Syncope in a patient with IM should bring to mind splenic rupture, and as long as the spleen is enlarged, the risk of rupture persists.

Neurologic complications are rare but aseptic meningitis, meningoencephalitis and peripheral neuropathies have been reported.

Airway obstruction from massively enlarged tonsils and pharyngeal edema may occur. *Pneumonitis* is seen on chest x-ray films in 2 percent to 5 percent of patients and *pleural effusions* are noted.

Severe *thrombocytopenia* due to increased platelet destruction can occur. *Anemia* is rare and, when present, the cause is hemolysis due to cold agglutinins directed against red cell antigen i. The direct Coombs' test may be positive.

Cardiac complications with nonspecific electrocardiographic changes, pericarditis and myocarditis can occur.

Differential Diagnosis

If patients with the clinical triad of lymphadenopathy, fever and sore throat have atypical lymphocytes and a positive heterophil test, the diagnosis of EBV mononucleosis is established. Difficulties arise when typical clinical features of IM are observed with repeatedly negative heterophil tests, more common in the pediatric population. Most of these patients have significant antibody titers to EBV, suggesting that the disease is still due to the virus. Other causes of heterophil-negative mononucleosis are CMV and toxoplasmosis. CMV follows transfusions more frequently than does EBV, and sore throat is not a major feature. Viral hepatitis may present with low-grade fever and lymphadenopathy, but is also not accompanied by pharyngitis. Streptococcal sore throat may be confused with IM. Here, lymphadenopathy is anterior cervical and splenomegaly is absent; in some cases, the two diseases coexist. Drug-induced hypersensitivity reactions, particularly the lymphadenopathy associated with recent institution of phenytoin, may be excluded by the history.

The most worrisome differential diagnosis is lymphoma or leukemia. Anemia is more common in the malignant disorders. Hyperuricemia should not be used as a laboratory test to differentiate between lymphoma and IM, as it can be seen in the acute phase of mononucleosis.

Treatment

The treatment of IM is mainly supportive because more than 95 percent of patients recover uneventfully without specific therapy. Isolation is unnecessary and during the acute phase of the illness, bed rest is encouraged though patients' symptoms govern the degree of activity. Gradual increase in activity beginning a week after a patient becomes afebrile and spanning a three- to four-week period is prudent, but vigorous activity should be avoided for three to six months to prevent splenic rupture. Patients should be advised to contact their physician immediately if abdominal pain develops.

Aspirin or acetaminophen is helpful for the control of fever and headache, and saline or lidocaine gargles relieve the sore throat. There is no indication for the routine use of antibiotics in IM. If their use becomes necessary due to a concomitant streptococcal pharyngitis, administration of ampicillin should be avoided because of the high incidence of rash.

Corticosteroid therapy should be reserved for

severe manifestations or complications of the disease, such as impending airway obstruction, hemolytic anemia, severe thrombocytopenia, considerable neurologic involvement and myocarditis. Prednisone in dosages of 60 to 80 mg a day is given. Because the response is usually rapid, the dosage may be tapered over one to two weeks.

Transfusions are seldom necessary in uncomplicated IM. If required they should be given at 37°C because a patient with anemia nearly always has cold agglutinins.

Finally, because the EBV can be cultured for several months from a patient's lymphocytes, blood donation should be postponed for at least six months after the onset of the illness.

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Fifth National Impaired Physician Conference

PHYSICIAN IMPAIRMENT and its effect on patients, families and colleagues is the subject of the American Medical Association's Fifth National Conference on the Impaired Physician, to be held September 22 through 25, 1982, in Portland, Oregon. The meeting is cosponsored by the Oregon Medical Association and the Multnomah County Medical Society and will be held at the Portland Marriott.

TABLE 1.—*Hospital Source That Provided Infant Passenger Safety Information (53 Hospitals)**

Nature of Infant Passenger Safety Information	*Nurse*	*Pediatrician*	*Pediatric Nurse Practitioner*	*Health Educator*	*Volunteer*	*Obstetrician*	*Other Personnel*
	Number of Hospitals						
Distribution of written materials	21	7	6	4	3	1	7
Discussion with parents	19	11	9	4	1	1	1
Included in discharge instructions	11	8	6	..	..	..	1
Audiovisual materials	8	2	..	1	1	..	1
Display of child car seat	5	2	1	1	1	..	..
Demonstration of car seat use	5	1	1	..	1	..	1
Posters	2	..	..	..	..	..	..

*The person who completed the questionnaire was identified in only 53 hospitals, but in some hospitals more than one source provided the information.

and six reported that they had fewer than 30 deliveries in 1979. Thus, the final study sample comprised 195 hospitals. Of these, 166 hospitals returned completed study forms, for a response rate of 85.1 percent.

In all, 39 directors of nursing provided the information (23.5 percent of the responses); the other respondents included 76 nursing supervisors (45.8 percent), 26 nursing coordinators (15.7 percent), 9 clinical nurses (5.4 percent), 7 nurse administrators (4.2 percent), 5 nurse educators (3.0 percent) and 4 other nurses (2.4 percent).

Provision of Infant Passenger Safety Information

The hospitals were asked "Does the Perinatal Service (inpatient maternity and newborn service) *routinely* provide information on infant car-safety to the parents of newborns?" Of the 166 responding hospitals, 53 (31.9 percent) answered "Yes."

The nature of the infant passenger safety information provided by the reporting hospitals was as follows: distribution of written materials (77.4 percent), discussion with parents (73.6 percent), part of discharge instructions (41.5 percent), use of audiovisual materials (28.3 percent), display of infant car seat (20.8 percent), demonstration of car seat use (17 percent) and posters (3.8 percent).

Table 1 shows which hospital personnel provided what type of infant passenger safety information. Nurses, pediatricians and nurse practitioners were the principal informants. Health educators, volunteers and obstetricians were involved in a very limited way.

Other Services Offered

Three hospitals had infant car seats available for purchase, each with a different model: a Bobby-Mac (Dept. 60, Box 209, Scarsdale, NY 10583), a Strolee (19067 South Reyes, Compton, CA 90224) and a Trav-L-Guard (Century Products, 1366 Commerce Dr., Stow, OH 44224). Fourteen hospitals provided a listing of stores in the community that carried car seats for sale, and ten hospitals provided a price list of the various infant car seats commercially available. Not a single hospital, however, had a car seat loaner program.

Interest in Developing Comprehensive Program of Infant Passenger Safety

All hospitals were asked the following question: "Could your present program (education) be developed into a comprehensive program of infant car safety education that could be incorporated into the existing inpatient Perinatal Service program for parents?" Of 163 hospitals responding, 115 or 70.6 percent answered "Yes."

The type of information recommended by those hospitals interested in developing a comprehensive program included distribution of written materials (73 percent), audiovisual materials (53.9 percent), car seat demonstration (23.5 percent), discussion with parents (10.4 percent), posters (6.1 percent) and written materials in Spanish (6.2 percent).

Hospitals Not Interested in a Comprehensive Program

Of 166 hospitals 48 (28.9 percent) were not interested in developing a comprehensive program

of infant passenger safety. Reasons given for this decision were as follows: insufficient time (37.5 percent), insufficient personnel (16.7 percent), no interest at present (8.3 percent), education should be included in childbirth classes (6.3 percent), education should be provided in pediatric offices (6.3 percent) and other reasons (12.5 percent).

Estimated Percentage of Infants Safely Restrained

Table 2 shows the estimated percentage of infants for whom passenger safety restraint was provided at the time of hospital discharge. Only 25 of the hospitals (less than 18 percent) estimated that 25 percent or more of the discharged infants were safely restrained.

TABLE 2.—*Infants Estimated to Be Safely Restrained in Car When Leaving Hospital (141 Hospitals Reporting)*

Infants Safely Restrained percent	*Hospitals (N=141)* Number	(Percent)
0	45	(32.0)
1-25	71	(50.3)
26-50	19	(13.5)
51-75	4	(2.8)
76-100	2	(1.4)
TOTAL	141	(100.0)

TABLE 3.—*Provision of Child Car Passenger Safety Information by Hospital Births, Location and Sponsorship*

	Number of Hospitals	*Hospitals Providing Car Safety Information* Number	(Percent)	
Births per year				
Fewer than 500	55	12	(21.8)	
501 to 1,000	39	10	(25.6)	
1,001 to 2,000	51	20	(39.2)	
Over 2,000	18	11	(61.1)	
				$P<.01$
TOTAL	163			
Geographic location				
Major metropolitan	70	24	(34.3)	
Lesser metropolitan	44	19	(43.2)	
Adjacent	31	8	(25.8)	
Rural	20	2	(10.5)	
				$P<.10$
TOTAL	165			
Sponsorship				
District	33	7	(21.2)	
Public	28	6	(21.4)	
Voluntary	70	30	(42.9)	
Proprietary	24	6	(25.0)	
Governmental	10	4	(40.0)	
				$P<.09$
TOTAL	165			

Additional Comments Made by Hospital Respondents

In all, 16 hospitals mentioned that they would like infant passenger safety to be included in childbirth education classes, and 14 hospitals requested written materials for distribution. Another 11 hospitals stated that there is need for additional public education on this subject. Nine hospitals recommended that most of the education be provided in pediatricians' offices.

Correlation of Hospital Births, Geographic Location and Sponsorship With Infant Passenger Safety Education

The hospital's annual (1978) number of births, its geographic location and its sponsorship were cross-tabulated for provision of infant car-safety information and the desire to develop a comprehensive program (Tables 3 and 4). A higher number of births appears to be associated with a greater provision of infant passenger information. A higher number of births is also associated with a greater interest in developing a comprehensive program of infant passenger safety.

Discussion

This survey of infant passenger safety programs in perinatal services in California indicates the

TABLE 4.—*Hospitals Interested in a Comprehensive Infant Passenger Safety Program—By Births, Location and Sponsorship*

	Number of Hospitals	*Hospitals Interested in Comprehensive Program* Number	(Percent)	
Births per year				
Fewer than 500	54	32	(59.3)	
501 to 1,000	38	33	(86.8)	
1,001 to 2,000	50	36	(72.0)	
Over 2,000	18	11	(61.1)	
				$P<.04$
TOTAL	160			
Geographic location				
Major metropolitan	69	49	(71.0)	
Lesser metropolitan	42	31	(73.8)	
Adjacent	31	20	(64.5)	
Rural	20	14	(70.0)	
				$P<.51$
TOTAL	162			
Sponsorship				
District	32	22	(68.8)	
Public	28	15	(53.6)	
Voluntary	69	50	(72.5)	
Proprietary	23	18	(78.3)	
Governmental	10	9	(90.0)	
				$P<.1$
TOTAL	162			

limited extent of the existing programs. Less than a third of the hospitals routinely provide some infant passenger safety education. The respondents' estimate of infant car seat use at the time of hospital discharge is also low. Less than one of five hospitals estimate that over 25 percent of the infants ride home safely restrained.

There is keen interest, nevertheless, in the subject of infant and child car-safety and in doing more in this area while the mother and infant are in hospital. Seven of ten hospitals are interested in making their present limited program more comprehensive or, if a program is lacking, to initiate one. At the very least, they would start distributing written materials and using audiovisual aids. A few hospitals have shown strong commitments by compiling a list of retail stores and current prices. Three have persuaded their pharmacy or gift shop to stock car seats and to sell them. No hospital has yet shown an interest in initiating a car seat loaner program.[9]

Of interest are the reasons given by several hospitals for not doing more at this time. The main limitations are insufficient personnel and time. As would be expected, hospitals with few deliveries are not as interested in infant passenger safety education. Also, the recent trend toward earlier discharge of newborns necessitates the setting of priorities for parent education objectives. There is reluctance to introduce infant passenger safety education when there is hardly time to discuss other more traditional subjects such as infant feeding, bathing, immunizations and so forth.

Because of the above reasons, a number of respondents suggested that infant passenger safety education should be introduced either in childbirth preparation classes or in discussions at pediatricians' offices, rather than in the newborn nursery. Childbirth classes would seem to be an ideal setting but, regrettably, the percentage of expectant parents attending these is limited. Greater efforts in pediatricians' offices certainly seem to be indicated,[10] as some of these activities have been shown to be effective.[11]

Because the vast majority of infants are born in hospitals, health education efforts in this setting still have the greatest potential of motivating the parents to practice infant passenger safety. An organized plan is needed that would assist hospital staff to implement more comprehensive activities in conjunction with the functions of childbirth educators, parent educators, obstetricians, pediatricians, family practitioners, nurses, nurse practitioners and hospital-based health educators. Programs such as Project Childsafe initiated by the National Safety Council; the "First Ride, A Safe Ride" program in Washington state, and its national counterpart sponsored by the American Academy of Pediatrics would address some of these needs. Outside the hospital, infant and child passenger safety needs further promotion by local and state departments of health, state offices of traffic safety, state departments of motor vehicles, automobile associations, and the National Safety Council.

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'Loads' Alert

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"Loads," a combination of glutethimide and codeine, are a relatively new form of drug abuse that is increasing in popularity in the Los Angeles area as a heroin-substitute. Preliminary findings based on interviews and treatment of a group of preferential Loads abusers seen over a one-year period suggest that this combination has a potential for serious intoxications and withdrawal complications. The common withdrawal symptoms include those produced by both a sedative-hypnotic and a major narcotic and necessitate a detoxification plan based on the pharmacologic rationale of the abused combination.

IN THE WORLD of drug abuse there are many fads whose popularity and longevity depend on complex interactions between biosocial and economic factors. When the availability and quality of heroin are poor (and invariably the cost expensive), the drug culture experiments with various combinations to produce a comparable "high."[1-5] Currently in the Chicago area, the heroin-substitute is "T's and blues" (Talwin [pentazocine] and Pyribenzamine Hydrochloride [tripelennamine]).[4] In Los Angeles and surrounding areas it is "Loads" (glutethimide and codeine phosphate).[5] One Loads contains two tablets of glutethimide (totaling 1 gram) and four tablets of codeine No. 4 (240 mg); the latter are typically Empirin No. 4 (aspirin, 325 mg, and codeine, 60 mg) or Tylenol No. 4 (acetaminophen, 300 mg, and codeine, 60 mg). Although a dosage variant of this combination was reported over a decade ago,[1] there is little information available on the characteristics, treatment or potential complications of this relatively new drug combination.

The present investigation was undertaken at the Metropolitan State Hospital Drug Abuse Program (Norwalk, California), a major inpatient state-operated drug abuse, detoxification, evaluation and rehabilitation program servicing the Los Angeles metropolitan adult population. The drug detoxification service is used primarily by heroin-dependent patients. During the two years before this investigation we had admitted fewer than ten patients to this service who had claimed a Loads habit. However, over the past 12 months we have admitted 89 patients seeking detoxification from Loads (see Table 1). The following are the demographic characteristics of these patients: men, 60 percent and women, 40 percent; mean age, 27 years (range, 19 to 42); caucasians 80 percent, hispanics 16 percent and blacks 4 percent. For comparison, our typical heroin patient is 30 years of age, the male-to-female ratio is 3:1 and race is primarily hispanic, followed by caucasians and blacks. Of the 89 Loads patients, 65 were interviewed extensively to determine characteristics of Loads abuse; that is, prior favorite drug habit, withdrawal history (if previously attempted without medical supervision) and withdrawal symptoms, and significant problems encountered while taking Loads (accidents, and so forth).

Loads are ingested orally to produce an intoxication that is claimed to be an equivalent or better

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TABLE 1.—*"Loads" Admissions From November 1980 Through October 1981*

	11/80	12/80	1/81	2/81	3/81	4/81	5/81	6/81	7/81	8/81	9/81	10/81	Total
Number opiate admissions	93	104	136	110	154	129	142	138	106	81	74	82	1249
Number other* admissions	11	2	13	16	13	13	11	16	20	16	33	28	213
Number "Loads" admissions	1	3	4	3	5	6	5	5	15	7	12	23	89
"Loads" as percent of all admissions	1.0	2.7	2.6	2.3	2.8	4.1	3.2	3.1	10.6	7.2	10.1	17.3	5.7

*Phencyclidine hydrochloride (PCP), amphetamine, phenobarbital, cocaine or LSD.

ABBREVIATION USED IN TEXT

APC = aspirin, phenacetin and caffeine

"high" than that obtained with heroin. Most of our patients previously used heroin, but gradually shifted to Loads. Although the typical intravenous "rush" (or sudden onset) is absent, it can be approximated when Loads are taken on an empty stomach. Our patients reported that the intoxication is achieved within 20 minutes after ingestion, with the peak effect occurring after 40 minutes. Concurrent ingestion with ethanol reportedly intensifies this rush, suggesting an increase in the rate of drug absorption. The Loads-intoxicated state resembles that produced by ethanol and barbiturates and is characterized by alternating states of dream-like euphoria and "nodding." The latter term is commonly used in the drug culture to describe the somnolent part of this experience and is related to the soporific and stupefying effects of the drugs. Nodding is at times associated with brief or prolonged sensorimotor disturbances in the extremities and many of our Loads subjects had either experienced or presented with such disturbances.

In the beginning of this habit, the intoxication high reportedly persists for an average of 12 hours but increasing tolerance reduces it to three hours. In one patient, tolerance resulted in a habit requiring up to 12 Loads ingestions a day. These amounts are much higher than those previously reported[2,3] so that the potential for serious intoxications and difficult withdrawals is obvious. Most patients took one Loads daily at the start of the habit and were ingesting over three Loads just before detoxification. They gave a mean time interval of 24 hours between the last Loads ingestion and the beginning of withdrawal symptoms. Many of these patients had tried to withdraw from Loads themselves on a previous occasion, but apparently none were successful. Many of our patients encountered significant problems while taking Loads, such as coma, convulsions, peripheral neuropathies and major accidents, including automobile crashes, cuts and burns.

The persons under investigation also reported substitutions in the event of temporary unavailability of glutethimide or codeine: generally, another sedative-hypnotic for glutethimide, and another narcotic analgesic for codeine. The codeine is invariably taken as Empirin No. 4, Tylenol No. 4 or Tabloid APC (aspirin [227 mg], phenacetin [162 mg] and caffeine [32 mg]) with codeine No. 4 (60 mg). However, these substitute combinations are claimed to be less attractive than Loads. Some people stated that combining diazepam (Valium), 10 mg, with Loads expanded the peak period of the high and decreased the number of Loads needed to achieve the desired euphoric effect. Most people, however, categorically denied combining Loads with anything else, having known or heard about others who have died when mixing Loads with alcohol or other drugs. In Southern California, Loads were responsible for at least seven deaths during the first five months of 1981 (Los Angeles *Times,* August 14, 1981, p 19).

The commonly observed withdrawal symptoms include anxiety, sweating, severe headache, palpitations, insomnia, fever, abdominal pain, muscle spasms, diarrhea, vomiting, rhinorrhea, tremors, involuntary jerking movements of the limbs and convulsions. To provide a safe detoxification and prevent withdrawal reactions, we adopted two treatment regimens based on the pharmacology of this drug combination. After establishing the accuracy, duration, dosage and other aspects of the habit, we convert glutethimide and codeine doses to equivalent amounts of phenobarbital and methadone hydrochloride (500 mg of glutethimide

equals 60 mg of phenobarbital; 120 mg of codeine equals 10 mg of methadone). From a third to the full dose equivalent of converted glutethimide to phenobarbital is given for the first two to three days until a patient is drug free, after which the patient is observed carefully for another three days. The amount of phenobarbital given depends on the severity of the addiction and the presence of withdrawal symptoms. Methadone is given in a third of the dosage conversion on a twice-a-day decreasing scale over the first five to seven days of treatment.

Some variations in the above schedule are made depending on the total daily quantity abused and the duration of the habit. In general we have used a 15-day withdrawal schedule for habits of three or more Loads a day and of more than 60 days' duration, and a 10-day schedule for habits of lesser amounts and duration. To date we have had satisfactory results.

The medical community should be aware that this type of abuse can present in many different ways such as visits for prescriptions, intoxication ranging from ethanollike disinhibition to severe poisoning characterized by deep, cyclical coma or presentation in an emergency room following an accident. Because large amounts of aspirin or acetaminophen (also phenacetin and caffeine in APC preparations) are consumed as part of Loads, a clinician should be alert to possible salicylism, hepatotoxicity or analgesic nephropathy. We have seen patients with salicylate concentrations ranging from 6 to 14 mg per dl in blood specimens drawn two days or more after the last reported Loads ingestion. Glutethimide may also cause hypocalcemia,[6] osteomalacia,[7] peripheral neuropathy and cerebellar impairment,[8] and poor response to chronically prescribed medications (for example, warfarin) as a result of enzyme induction.[9] Determinations of glutethimide concentrations in blood may be helpful in identifying this type of abuse. We recommend that urine be analyzed also because highly tolerant abusers may have nondetectable blood concentrations due to the rapid disappearance of glutethimide from their blood.

The attractiveness of Loads over heroin may be explained by the potent enzyme-inducing property of glutethimide that converts more codeine to morphine than the usual 10 percent after therapeutic analgesic doses.[10] Thus, glutethimide may be able to transform a normally minimally abused narcotic with high side-effect profile and low affinity for the opiate receptor into a potent agonist. Glutethimide also stimulates its own metabolism, and conversion to the more potent and toxic 4-hydroxy-glutethimide may explain the seriousness of overdose and reported fatalities, particularly when combined with ethanol.

We believe that this combination has a potential for widespread abuse. Whether the knowledge of the potentially lethal effects of Loads exerts any curtailment of this spread remains to be seen, and may depend on the continued availability of glutethimide and heroin. The medical community should be aware of the increasing abuse potential of glutethimide. We ourselves have difficulty understanding the continued prescribing of glutethimide as a hypnotic in 1982.

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The Bedside Sherlock Holmes

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There are a multitude of diagnostic clues contained in clothing, jewelry, possessions and other extracorporeal attachments that each patient brings with him or her to a physician. Because of the emphasis of classic physical diagnosis on the body of a patient solely, and because of modern practices that may have patients stripped of these articles before the first encounter with their physician, these interesting and enlightening findings are often ignored or unavailable. Incorporation of these observations into the panoply of data obtained from the history and physical examination will enhance both the accuracy and adventure of differential diagnosis. Such exercises in observation, moreover, may increase general physical diagnostic skills as well as enliven bedside rounds.

SHERLOCK HOLMES: *"Let him, on meeting a fellow mortal, learn at a glance to distinguish the history of the man and the trade or profession to which he belongs. By a man's finger-nails, by his coat-sleeve, by his boot, by his trouser knees, by the callosities of his forefinger and thumb, by his expression, by his shirt cuffs—by each of these things a man's calling is plainly revealed."*

JOHN H. WATSON, MD: *"What ineffable twaddle!"*

A. CONAN DOYLE
A Study in Scarlet

An emergency room physician is often confronted with a patient who can give no history: a coma or aphasia victim; one who speaks a language unfamiliar to the physician; a person in a toxic condition, or a confused, mute or manipulative man or woman. In such circumstances we are most aware that a good history is the bedrock of the diagnostic process.[1] But even in calmer situations than emergency room encounters, experienced clinicians know that the keener one's physical observations, even from the first instant of patient contact, the better the historical questions asked.[2] Conversely, the history signals the clinician what to look for on physical examination.

We physicians are trained in a systematic, logical approach to physical diagnosis of the human body. Unfortunately, the conditions under which such examinations may occur can exclude a variety of invaluable observations that provide clues to a patient's state. In a busy contemporary office practice, the first meeting between a patient and physician may be with the patient already stripped and gowned to save time. In hospitals, an almost invariable initial feature in the process of admission is to whisk away a patient's property—clothes, jewelry, wallet or purse—for safekeeping. This robs a diagnostician of a rich

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source of physical evidence and may leave a house officer and medical student, in particular, unaware through their entire training of the value of these articles as repositories of information. The inattention to the usefulness of these aids to physical diagnosis is such that even when patients are in possession of their belongings at the time they are seen, the personal effects tend to be ignored.

Only occasionally alluded to in textbooks on physical diagnosis, scattered through the medical literature as letters to editors or buried as "pearls" in the body of larger articles, these bits of diagnostic acumen are not readily available in any systematized format. Over the years we and other clinicians have noted, but never to our knowledge organized, the multitude of clues available from unconventional sources. We attempt here a review to highlight some of these fascinating, at times enjoyable but little-celebrated, "extracorporeal" findings.

Clothing

A patient who arrives at the door of an emergency room in street clothes during daylight hours is less likely to be chronically ill than one who comes already clad in pajamas or nightgown. Transfer from another hospital is easily deduced if a patient is dressed in a hospital gown. People who bring suitcases with them to an emergency room anticipate admission; house staff recognize this as the *positive-suitcase sign,* said to be especially common in Veterans' Administration facilities.

The clothes a patient wears, and how they are worn, give clues to his or her socioeconomic status and cultural background, as well as state of health. An expensive-looking suit frayed at the edges may tell of a gradual decline in fortune. If all the labels in clothing are from a foreign country, recent immigration or travel may be assumed until otherwise contradicted. A victim's occupation may be pertinent to diagnosis and can sometimes be surmised from clothing: uniforms of all sorts are automatically revealing. Also of value are the characteristic stains on the clothing of a painter or butcher, the encrustations on a farmer, the soot of a coal miner, the smudges on a firefighter or the equipment belt of an electrician or carpenter.

The pattern of a man's tie may indicate his hobbies (tennis raquets, golf clubs, sailboats), club memberships and even occupational logos. A neck scarf on a woman may conceal her thyroidectomy or tracheostomy scar and broad-brimmed hats or long sleeves may suggest photosensitivity. Long sleeves inappropriate to the weather may also be used to cover the *track marks* of parenteral drug abuse or the scars of former suicide attempts.

A dominance of snaps and zippers in the place of buttons can reflect fashion, but also serves the utilitarian purpose of making dressing easier for those with loss of digital dexterity from arthritis or motor disease. Bizarre combinations of color in otherwise conservative clothing hint at color blindness in a man. In all of these assessments, however, an examiner must take into account the vagaries of American taste.

The degree of tidiness in which a person maintains his or her appearance may be simply a matter of habit or preference but can also reflect general well-being; people tend to be less attentive to their dress as they feel more ill.[3] A woman who took meticulous care with her clothes in the morning, for example, is less likely to have a debilitating chronic illness than an acute event that accounts for her admission to hospital that afternoon. The general fit of the clothes will tell of weight loss or gain, an important consideration in many diagnostic problems. Cerebral dominance (as in a stroke victim) may sometimes be inferred from the greater wear and tear on the shirt cuff on the side of handedness. A patient with hypothyroidism may be too warmly dressed for the weather, as one with hyperthyroidism is too lightly clad for the cold. Clothing may even contribute to the genesis of medical problems, as in an elderly person who is heavily bundled up in the summer and suffers heatstroke[4] or, the converse, a hypothermic sufferer from exposure with flimsy clothes.[5] Less dramatically, but important to a patient, a physician may counsel a woman with hiatus hernia symptoms to abandon her too-tight girdle.[6]

Perhaps most useful to an emergency room physician are the diagnostic usages of stains on the clothes of an unconscious patient. Blood stains immediately precipitate a search for their site of origin. The stains of vomitus are examined for color: the coffee-ground appearance of gastric bleeding is familiar to most doctors, as is bright red hematemesis. Red vomitus may also reflect regurgitation of a variety of red-colored foodstuffs (strawberry gelatin dessert, beets, port wine and so forth). A startling blue vomitus occurs

with iodine ingestion when the stomach contains carbohydrates.[7(p115)] The characteristic odors of vomitus and other excrement associated with certain disorders are discussed in the "Effluvia" section.

Underclothing should be examined for stains of stool and urine, which provide evidence of the color and odor of these, in some cases even when a patient is unable to produce a more adequate specimen for inspection. The presence of incontinence itself may be of clinical diagnostic importance and the quality of the incontinence material even more useful. A black stool stain can suggest melena, but can also reflect a patient's use of iron, charcoal, bismuth, black cherries[8] or even licorice ice cream.[9] Acholia may be diagnosed from the undershorts and, rarely, the silver stool of carcinoma of the ampulla of Vater (said to be an admixture of melena with acholic steatorrhea).[10] The dramatic smoking stools of yellow phosphorus poisoning are uncommon but of immediate import when they occur.[11]

Urine stains come in a variety of colors.[12-14] They may be red, as in hematuria and porphyria or the ingestion of pyridium, beets, phenolphthalein, aniline dyes or rifampin. Brown urine occurs with hemoglobinuria; myoglobinuria; methemoglobinuria; bilirubinuria, and the ingestion of phenol, cresol or phenylhydrazine. A black urine stain is the hallmark of alkaptonuria. Orange urine can be seen in patients who have eaten large amounts of rhubarb or senna or who are taking phenazopyridine hydrochloride (Pyridium). An extraordinary green or bluish urine may result from *Pseudomonas* infection or the use of indigo carmine, phenol, methylene blue or indigo blue dyes. Yellow-orange crystals in the diapers of children with Lesch-Nyhan syndrome may alert mothers and physicians of the infants to their uricosuria.[15]

Inspection of a handkerchief or paper tissues can convey the color and odor of sputum or tears. Both can be visibly yellow in a jaundiced patient. Anchovy or chocolate brown sputum suggests amebic abscess of the liver eroded through to lung.[16] Infected sputum may be green with *Pseudomonas,* rusty red with hemoptysis[7(p103)] or simply purulent yellowish grey. Red-tinged sputum, saliva and tears occasionally occur with the ingestion of rifampin.[17] Blood in the tears occurs with epistaxis, tumors of the lacrimal sac and with rare vicarious menses in women.[18] A feculent odor to sputum on a handkerchief suggests anaerobic lung abscess.

Sweat stains, especially in the axillary and inguinal regions, can be diagnostically helpful. Red-tinged sweat occurs in some patients taking rifampin and brown sweat may stain the clothes of patients with ochronosis.[19] The absence of sweat marks on the clothing of a patient with notable hyperpyrexia may suggest anhidrosis as a possible contributing factor to heat stroke.[20]

Small burn holes in the clothes occur in certain occupations such as welding or steelwork. Inattentive smokers also tend to burn their clothes. When the holes form in a necklace pattern around the collar, they are analogous to the *rosette sign* of skin burns caused by cigarettes when the smoker is "on the nod" from narcotics, alcohol or sedative abuse.[21] Obviously the location of evidence of violent trauma on clothing, such as bullet holes, slashes and powder burns, has forensic as well as immediate importance.

Inspection of the shoes is among the most revealing and least used of all aspects of diagnostic clothing analysis. As with other articles of clothing, shoes tell a story about their owner: work shoes on an accident victim, for example, suggest a different circumstance for an acute event than slippers, dress shoes, hunting boots or running shoes. The presence of one slipper and one shoe or of an open-toed shoe implies gout, trauma, other arthritis or bunions on the unshod foot. Shoes without laces, or laces undone, are more comfortable to an edematous or inflamed foot. Patients with Parkinson's disease or other motor limitation may simply lack the dexterity and flexibility to tie their shoelaces. A prosthetic shoe lift is a more obvious clue to a chronically shortened leg than simple inspection of a supine patient. The pattern of wear on the soles of shoes testifies to gait. For example, a rapid distinction between old and new hemiparesis in a patient in an emergency room can be achieved by examining the shoes, in which the differential wear of a long-standing limp is clear. Does a patient have a backache? A glance at new or very high-heeled shoes may solve the diagnostic mystery. In a patient with diabetes, the source of sepsis may be clarified by blood and serum stains seen on socks or by the presence of ill-fitting shoes.

Belts can be used to assess the rate and amount of weight change. Particularly telling are new belt holes made by a patient to allow for the expansion of the belly in ascites, for example, or the

diminution of girth in severe weight loss. The degree of wear around each belt hole, the recentness of new holes and cracks in the leather formed through long wear at a given girth allow a careful observer to estimate the rate of loss or gain.

With all clothing a caution must be given: A down-and-out patient, especially, may have obtained these articles at a second-hand shop. A clinician should not be led astray by diagnosing a disorder of the previous owner rather than of the current patient.

Jewelry

The amount of jewelry worn and its quality speak of both the economic status and the taste of the owner. Most observers know the obvious signs of marriage given by a wedding ring; fewer will recognize that the untanned area on the left fourth finger in a suicidally depressed patient, for example, may suggest that recent divorce or disillusionment motivated the desperate act. Loose rings, often wrapped with bandage or string to keep them on, tell of weight loss. Too-tight rings occur in edema and acromegaly. High school and college rings advise a clinician of a patient's educational level and club or organizational rings (Masons, Marine Corps and the like) of interests and past or present associations. It has been reported that black staining under a golden ring occurs in diabetes mellitus[22]; perhaps this more often is a clue about the metal than the patient wearing it.

Tie tacks, pins, medallions and cuff links tell of hobbies, clubs, education (Phi Beta Kappa) and even profession (American College of Physicians) and can provide a baseline for mental status examination. Medallions also give formal medical information, as may bracelets and anklets designed specifically for that purpose. Necklaces and medals may be all that testify to the religious beliefs of a critically injured or ill patient, should they wear a cross or Star of David. Family names, relationships and dates may be inscribed on medals, watches and bracelets. Copper bracelets suggest that a patient suffers from arthralgias or arthritis and believes that these talismans are therapeutic.

Few middle-class businessmen wear earrings, and their presence on a man bespeaks a certain life-style, as do nose rings in both men and women. Watches can, rarely, tell the time of an accident—the classic broken timepiece of detective fiction. Large numbers on the watch face suggest diminished acuity of vision in the owner. A braille watch face, when noticed, provides a readier answer to unresponsive pupils in a comatose patient than extensive neurologic testing. A hearing aid similarly alerts a clinician to decreased hearing in a patient and implies a chronic rather than acute hearing loss.

Wallet, Purse and Pocket

In an unconscious or delirious patient, exploration of personal effects (best done with a witness present) to establish identity is common practice in emergencies. For a trained observer, careful consideration of the contents of wallet, purse and pockets can yield much of both diagnostic and therapeutic benefit. Likewise, the physician who does a "wallet biopsy" for alert patients, with their permission and in their presence, can be rewarded with valuable information.

The implications are obvious if a patient bears a medical information card, doctor's appointment slip or health organization membership card. Prescription and over-the-counter drugs tell part of a patient's history and may, by their side effects, contribute to a user's current distress. Chewing tobacco can correlate with hypertension, hypokalemia and other signs of mineralocorticoid excess,[23] as can large amounts of licorice candy[24]; both contain glycyrrhizic acid, structurally similar to aldosterone. Licorice myopathy and myoglobinuria have also been reported.[25] Patients with diabetes or periodic hypoglycemia may carry a purse full of candy bars or sugar packets. Cigarettes in purse or pocket hint at the cause of respiratory distress or malignant weight loss. Snuff can cause oral cancer,[26] and the discovery of a pipe or cigarette holder that a patient habitually tightly clenches in his teeth may explain temporomandibular joint pain.[27]

Letters and notes give an idea of a patient's social status and often of the person's state of mind. Handwriting can provide a clue to disease, as in the micrographia of Parkinson's disease[28] or the disarray of the script of the patient with hyperthyroidism.[29] Dated tickets and receipts will tell where patients have been and what they have been doing. A chronically ill person is unlikely to have recently attended a rock music concert, for example. Is there more food on a grocery receipt than seems plausible for one person?—perhaps the unconscious person has a large family. Has he or she a bill from a liquor store?—perhaps alcohol is a problem. A checkbook will provide

a running chronicle of activities over a period of several weeks and may even contain the victim's personal physician's name. Travel tickets and passports will tell where one has been, and numerous automobile, hotel or airline credit cards suggest frequent travel.

The driver's license with its photograph and record of height and weight give a patient's status at the date of issue of the license (although consideration should be given to the fact that some persons will declare a less than true weight to a clerk at a department of motor vehicles). Family and personal photographs are often carried in wallets and can alert a clinician to the presence of possible ancillary historians and provide a comparative appearance to assess a patient's current state. This may provide a diagnosis of acromegaly, for example. Photographs of family pets and hunting and fishing licenses can be helpful in the consideration of certain zoonotic diseases.

Union cards and club memberships offer a perspective of a patient in society. Even a social security card is informative. The first digit of the social security number denotes where it was issued: if a 0, for example, the card was issued in the Northeast; if a 1, in the Mid-Atlantic states; 2 and 3 signify Southeast or Midwest; 4 prefaces cards issued in the Southwest and southeastern states; 5 marks the Plains states and the Far West. If the first digit is a 7, the owner of the card was associated with the railroads. If 9 is the first number, the patient had been adjudged disabled or blind.

Makeup

The presence or application of makeup in a woman generally bespeaks wellness or at least improvement, if she's been sick, in her sense of well-being.[30] The heavy use of eyebrow pencil may obscure the loss of eyebrow hair in hypothyroidism,[31] leprosy,[32] syphilis,[33] or lupus erythematosus.[34] The care with which makeup is applied indicates motor coordination. The hemiagnosia of a stroke victim may be evident by the confinement of makeup to half the face. Horner's syndrome may present as running of makeup only on the unaffected side of the face on a very hot day. Bizarre or excessive makeup suggests a less than conservative personality or occupation, or even a disordered mental state.

The recency of a woman's hairdo or hair tint attests to the last time she felt reasonably well. Most depressed people do not have the motivation, nor can a chronically ill woman tolerate the time and noxious odors of a beauty shop or self-applied preparations. The length the hair has grown out since a procedure provides a rough estimation of the duration of sickness. The use of a wig in either sex may be a cosmetic convenience or may cover the alopecia of a number of disorders from stress to cancer chemotherapy.

Fingernail polish is informative. A fingernail normally grows at a rate of about 0.1 mm a day.[35] The distance between the base of the nail and the line of polish gives an approximation of the time of application—that is, when the patient felt well and steady enough to paint it on. Toenail polish speaks to a certain physical flexibility on the part of a patient, if she applied it herself, or to the existence of a friend or relative who applied it for her. Picking at nail polish is evidence of nervousness.

Perfume can be used to cover over unpleasant body odors (see below) but in the absence of use as camouflage can often be taken as a sign of subjective well-being.

The Bedside Table

An initial exercise in physical diagnosis for medical students has a senior clinician taking a group to a patient's bedside and asking them each to describe what they see. Almost invariably the students focus their attention exclusively on the patient, neglecting the tattle-tale survey of suspended bottles for intravenous administration, medication sheets and bedside table. Consider the difference in estimating the educational level of a patient who has only comic books, as opposed to a Dostoevsky novel, by the bedside. Technical journals reveal occupations and interests. Bibles are ubiquitous and may or may not reflect deep convictions in a patient. Photographs and greeting cards tell of family and friends and generally imply a hospital stay of more than a few days. Large amounts of hair clinging to a brush or comb indicate hair loss through disease or stress. Even when cigarettes or ashtrays are not visible, nicotine stains on dentures at the bedside attest to long-standing habituation to smoking. That the teeth are at the bedside and not in the patient's mouth should elicit an inquiry about their fit. Elderly persons with poorly fitting dentures can have this as the sole cause of profound weight loss. The mandibular growth of acromegaly can cause false teeth to be malaligned and so removed

from the mouth. And just feeling terribly ill may lead a patient to neglect putting in the dentures.

An alert student will sometimes diagnose cataract extraction from eyeglasses lying on the table, and a broken pair of glasses can go a long way toward explaining confusion in some elderly patients.

Sourball candies in a jar at the bedside are common with patients on the protein-restricted diets of hepatic or renal failure and have been reported as a sign of xerostomia in Sjögren's syndrome.[36]

Effluvia

The odor of a patient can be diagnostically useful.[37-39] A number of hereditary metabolic diseases in children can be suggested by the odor of a child or his excrement.[39] In adults hepatic failure sometimes generates a musty, sweetish smell, the fetor hepaticus. Care should be taken in diagnosing uremia to be certain a patient has not voided on himself to account for the uriniferous odor about him. The sweet aroma of acetone is a useful, if inconstant, concurrent of ketoacidosis. The sweat of schizophrenic patients reportedly has a characteristic odor.[40] Typhoid victims are said to smell like freshly baked bread and patients with diphtheria to exude a sweet breath.[37] A foul or feculent aroma may mark intestinal obstruction, esophageal diverticulum, lung abscess or intranasal foreign body.[38,41] Strong or offensive body odor may be associated with the increased sweating and skin oiliness of acromegaly[42] or the prohibition of deodorants that is part of the therapy for hidradenitis suppurativa.[39]

Bad halitosis occurs in dental disease, trench mouth and amphetamine abuse.[38] Other drugs can be betrayed by their odors: the bitter-almond odor of cyanide; the fruity, penetrating smell of chloral hydrate or paraldehyde[38]; the garlic smell engendered by the ingestion of yellow phosphorus,[11] arsenic, tellurium and selenium[43] or parathione,[38] among others, and the medicinal odor of penicillin. An odor of violets in the urine suggests turpentine poisoning[38] and it has been reported that urine odor can distinguish prerenal azotemia from acute tubular necrosis: in the former, the urine smells like concentrated urine and in the latter more like stale water.[44] The odor of alcoholic beverages is highly suspicious to clinicians, but may be obscured by the cover odor of breath mints[45] taken to disguise this evidence of alcohol use.

Whether a patient with an internal malignancy can indeed, as the ward saying has it, "smell like a cancer" begs investigation, but the necrosis of external malignant lesions can clearly give rise to disagreeable odors.[37]

Conclusions

Over centuries of medical practice, physicians have used extracorporeal diagnosis with as much enthusiasm as they have corporeal physical diagnosis. Though especially valuable in an uncommunicative or unconscious patient, extracorporeal clues can also stimulate a physician to diagnostic hypotheses in an alert patient. In these times of greater distance between patients and physicians, the loss of house calls, with their vast opportunities for extracorporeal observations, and the often automatic denudation of our patients before their first physician encounter, attention to these supplemental diagnostic techniques has waned. Because of this we fear that not only will their value be lost but, as great a pity, their fun as well.

We have no doubt omitted mention of many extracorporeal clues. Moreover, because of the nature of the literature recording these observations and because some were by word of mouth from our colleagues, we may have omitted reference credit to many who wrote of them before us. For this we apologize. Our greatest debt, of course, is to Sir Arthur Conan Doyle and to his teacher, Dr. Joseph Bell.

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in memoriam

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Mehlin, G. Burch, San Diego. Died May 7, 1982, in San Diego, aged 82. Graduate of St. Louis University School of Medicine, 1928. Licensed in California in 1929. Dr. Mehlin was a retired member of the San Diego County Medical Society.

Melody, George F., San Francisco. Died April 7, 1982, in Burlingame, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1940. Dr. Melody was a member of the San Francisco Medical Society.

Nelson, Leroy J., Eureka. Was killed March 31, 1982, in a snow avalanche at Alpine Meadows, aged 39. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1969. Licensed in California in 1975. Dr. Nelson was a member of the Humboldt-Del Norte Medical Society.

Patterson, John A., San Bernardino. Died April 5, 1982, in San Bernardino, aged 85. Graduate of the University of Toronto Faculty of Medicine, 1923. Licensed in California in 1924. Dr. Patterson was a retired member of the San Bernardino County Medical Society.

Pollack, Seymour, Los Angeles. Died April 8, 1982, in Los Angeles, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1945. Licensed in California in 1945. Dr. Pollack was a member of the Los Angeles County Medical Association.

Polland, W. Scott, San Rafael. Died April 3, 1982, in San Rafael of cerebrovascular accident, aged 77. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr. Polland was a member of the Marin Medical Society.

Porter, Clarence Chipley, San Francisco. Died May 15, 1982, aged 89. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1918. Licensed in California in 1923. Dr. Porter was a member of the San Francisco Medical Society.

Quinn, William F., Los Angeles. Died May 15, 1982, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1931. Dr. Quinn was a member of the Los Angeles County Medical Association.

Rapaport, Walter, Oakland. Died March 19, 1982, in South Lake Tahoe, aged 87. Graduate of Georgetown University School of Medicine, Washington, DC, 1919. Licensed in California in 1928. Dr. Rapaport was a retired member of the Alameda-Contra Costa Medical Association.

Reid, Robert Huestis, Los Gatos. Died June 9, 1982, in Los Gatos, aged 57. Graduate of the State University of New York College of Medicine, Brooklyn, 1948. Licensed in California in 1960. Dr. Reid was a member of the Santa Clara County Medical Society.

Risser, Joseph C., sr., Pasadena. Died March 11, 1982, in Pasadena of myocardial infarction, aged 89. Graduate of the State University of Iowa College of Medicine, Iowa City, 1923. Licensed in California in 1935. Dr. Risser was a member of the Los Angeles County Medical Association.

Rogers, William E., Santa Rosa. Died April 10, 1982, in Santa Rosa of cancer, aged 73. Graduate of the University of Louisville School of Medicine, 1938. Licensed in California in 1939. Dr. Rogers was a retired member of the Sonoma County Medical Association.

Rutherford, Miriam H., Oakland. Died March 23, 1982, aged 75. Graduate of the University of California Medical School, Berkeley-San Francisco, 1937. Licensed in California in 1937. Dr. Rutherford was a retired member of the Alameda-Contra Costa Medical Association.

Sandie, Joseph, Laguna Hills. Died February 22, 1982, aged 86. Graduate of Rush Medical College, Chicago, 1924. Licensed in California in 1924. Dr. Sandie was a member of the Los Angeles County Medical Association.

Still, Richard Mathias, Pacific Grove. Died April 22, 1982, in Pacific Grove, aged 73. Graduate of the University of Nebraska College of Medicine, Omaha, 1938. Licensed in California in 1948. Dr. Still was a member of the Monterey County Medical Society.

Weinstein, Hyman William, Encino. Died April 14, 1982, aged 83. Graduate of the Yale University School of Medicine, New Haven, 1923. Licensed in California in 1948. Dr. Weinstein was a retired member of the Los Angeles County Medical Association.

New Mexico Medical Society

Brown, Warren T., Albuquerque. Died May 10, 1982, in Albuquerque, aged 75. Graduate of the University of Texas Medical Branch, Galveston, 1933. Licensed in New Mexico in 1954. Dr. Brown was a retired member of the Albuquerque and Bernalillo County Medical Association.

Martin, John W., Gallup. Died April 21, 1982, in Gallup, aged 77. Graduate of Northwestern University Medical School, Chicago, 1950. Licensed in New Mexico in 1951. Dr. Martin was a member of the McKinley County Medical Society.

Weston, James T., Albuquerque. Died May 10, 1982, in Albuquerque, aged 58. Graduate of Cornell University Medical College, New York, 1948. Licensed in New Mexico in 1973. Dr. Weston was a member of the Albuquerque and Bernalillo County Medical Association.

Washington State Medical Association

Jordan, Richard, Rathdrum, Idaho. Died April 26, 1982, in Spokane of cerebral hemorrhage, aged 66. Graduate of the St. Louis University School of Medicine, 1947. Licensed in Washington in 1948. Dr. Jordan was a retired member of the Spokane County Medical Society.

Kraabel, Donovan O., Seattle. Died December 17, 1981, in Seattle, aged 79. Graduate of Northwestern University Medical School, Chicago, 1927. Licensed in Washington in 1928. Dr. Kraabel was a retired member of the King County Medical Society.

Lee, Albert Francis, Mercer Island. Died March 1, 1982, aged 71. Graduate of Duke University School of Medicine, Durham, 1937. Licensed in Washington in 1940. Dr. Lee was a retired member of the King County Medical Society.

Leonard, John Michael, Seattle. Died April 3, 1982, in Kauai, Hawaii, aged 42. Graduate of the University of Minnesota Medical School, Minneapolis, 1964. Licensed in Washington in 1969. Dr. Leonard was an associate member of the King County Medical Society.

Manning, James Howard, Denver, Colorado. Died February 17, 1982, aged 89. Graduate of Rush Medical College, Chicago, 1921. Licensed in Washington in 1921. Dr. Manning was a retired member of the King County Medical Society.

McLemore, Ira O., Seattle. Died March 10, 1982, aged 84. Graduate of the Medical College of Georgia, Atlanta, 1923. Licensed in Washington in 1927. Dr. McLemore was a retired member of the King County Medical Society.

Samman, Howard David, Seattle. Died January 30, 1982, in Seattle, aged 56. Graduate of the Universität Heidelberg Medizinische Fakultät, Baden, 1958. Licensed in Washington in 1960. Dr. Samman was a member of the King County Medical Society.

Sutton, Robert C., Seattle. Died December 4, 1981, aged 62. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1944. Licensed in Washington in 1954. Dr. Sutton was a member of the King County Medical Society.

Weitz, Henry E., Spokane. Died March 11, 1982, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in Washington in 1946. Dr. Weitz was a retired member of the Spokane County Medical Society.

USMA ANNUAL MEETIN

SPECIAL SESSION NO. 1 8:00 am
THURSDAY, SEPTEMBER 16, 1982

CARCINOMA OF THE BREAST

Problems of Differential Diagnosis of Controversial Breast Lesions
RAFFAELE LATTES, MD
Columbia-Presbyterian Medical Center
New York, New York

Primary Management of Carcinoma of the Breast
WILLIAM LAURENCE DONEGAN, MD
Medical College of Wisconsin
Milwaukee, Wisconsin

Adjuvant Treatment of Carcinoma of the Breast with an Emphasis on the Role of Estrogen Receptors
BARTH HOOGSTRATEN, MD
Medical Director
Cancer Treatment Center
Bethesda Hospital
Cincinnati, Ohio

Prophylactic Mastectomy and Breast Reconstruction Following Mastectomy
DONALD F. TEAL, MD
Eugene, Oregon

SPECIAL SESSION NO. 2 8:00
THURSDAY, SEPTEMBER 16, 1982

NEW DEVELOPMENTS IN CARDIOVASCULAR DISEASE

Calcium Channel Blockade in the Management of Cardiovascular Diseases
ELLIOTT M. ANTMAN, MD
Brigham-Women's Hospital
Harvard Medical School
Boston, Massachusetts

Prediction of Risk of Cardiovascular Morbidity an Mortality
SHAHBUDEN RAHEMTOOLA, MD
University of Southern California
Los Angeles, California

Angioplasty of Renal and Visceral Arterial Diseas
ERNEST J. RING, MD
Professor of Radiology
Director of Interventional Radiology
University of California
San Francisco, California

Heart Transplantation
STUART W. JAMIESON, MD
Assistant Professor of Cardiovascular Surgery
Director of Cardiac Transplantation
Stanford University School of Medicine
Stanford, California

FIFTH ANNUAL SKAGGS LUNCHEON

12:00 NOON

"WHAT'S NEW IN MY SPECIALTY"

Provocative brief overview of innovations in six specialty areas presented by guest speakers from morning sessions.

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OTHER GUEST SPEAKERS

NALD F. TEAL, MD
ene, Oregon
it Replantation" (Panel member)

E E. PEACOCK, Jr., MD
ne University School of Medicine
Orleans, Louisiana
malignant Breast Disease and Prophylactic
stectomy" (Panel member)

- ROD HESTER, MD
  Emory University
  Atlanta, Georgia
  "Premalignant Breast Disease and Prophylactic Mastectomy" (Panel member)
- BARTLEY R. FRUEH, MD
  Ann Arbor, Michigan
  "Blepharospasm: Diagnosis and Management"

SPECIALTY SCIENTIFIC SESSIONS

THURSDAY, SEPTEMBER 16, 1982 1:30 to 5:30 pm

ily Practice
ic Surgery

- Dermatology
- Ophthalmology
- Obstetrics and Gynecology
- General Surgery
- Pathology, Radiation Oncology

SPECIALTY DINNERS 6:00 PM HOTEL UTAH

ADDED FEATURES:

NESDAY, SEPTEMBER 15
idents' Reception and Dinner

FRIDAY, SEPTEMBER 17

Financial Planning Seminar	**9:00 am**
John Snow Memorial Lecture	**12:00 Noon**

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BOOK REVIEWS

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

FETAL HEART RATE MONITORING—Roger K. Freeman, MD, Medical Director, Women's Hospital, Memorial Hospital Medical Center, Long Beach, and Professor, Department of Obstetrics and Gynecology, University of California, Irvine; and Thomas J. Garite, MD, Associate Medical Director for Perinatology, Women's Hospital, Memorial Hospital Medical Center, Long Beach, and Assistant Professor, Department of Obstetrics and Gynecology, University of California, Irvine. The Williams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1981. 182 pages, $27.00.

The extensive clinical use of electronic fetal heart rate and uterine activity monitoring during the past decade has made a significant impact on the practice of obstetrics in this country. Since its widespread use has been so recent, many physicians responsible for patients in labor were not exposed to electronic fetal monitoring during their training. Much of the training in electronic fetal monitoring has been in postgraduate courses and other workshops. Heretofore, no comprehensive text has been available. This book makes a significant step towards filling that void. Our knowledge of electronic fetal monitoring is incomplete; nevertheless, the authors have condensed a large body of information into a very practical and readable text. An adequate bibliography is provided for those who wish to pursue specific topics in greater depth. The index is fairly comprehensive—however, an expansion of this part of the book would have been helpful.

The book presents a logical and practical approach to the use of electronic fetal heart rate and uterine activity monitoring. Chapters include the physiologic basis of fetal monitoring and the effects of hypoxia and asphyxia on the fetus and newborn. A very important chapter deals with the instrumentation itself, for, as the authors point out, to interpret fetal heart rate tracings accurately, it is important to understand the instrumentation used to accumulate, process and display the data. Other chapters deal with uterine contraction monitoring and basic pattern recognition of fetal heart rate tracings. There is also a chapter on the use of fetal acid base monitoring in conjunction with electronic fetal monitoring. One chapter deals with antepartum fetal monitoring including oxytocin challenge tests (OCT's) and nonstress tests (NST's). The techniques for carrying out these tests and evaluating their usefulness is presented.

The book is well illustrated with examples of fetal heart rate tracings which are clearly reproduced. Clinical histories along with appropriate monitoring tracings provide very useful information to the clinician.

The book is valuable not only as a text in the principles of fetal monitoring, basic through advanced, but also as a reference book. The information presented in this text should be familiar to everyone responsible for care of pregnant women in both the antepartum and intrapartum periods.

NEIL K. KOCHENOUR, MD
Chief, Maternal-Fetal Medicine
Assistant Professor
Department of Obstetrics and Gynecology
University of Utah College of Medicine
Salt Lake City

* * *

DRUG TREATMENT—Principles and Practice of Clinical Pharmacology and Therapeutics—Second Edition—Edited by Graeme S. Avery, Editor-in-Chief, Australasian Drug Information Services, Division of ADIS Press, Sydney & Auckland; Editor: **Clinical pharmacokinetics** and **Current Therapeutics**. ADIS Press USA, Inc., Building 3, Brooklyn Navy Yard, Brooklyn, NY (11205), 1980. 1,382 pages, $33.50.

The basic theme of the first edition of this book was the selection and use of drugs within a disease oriented context. Dr. Avery's book successfully filled a void in pharmacology textbooks that bridged the gap between those that either emphasize diagnosis and pathophysiology or pharmacology and therapeutics. The first edition was so successful, in fact, that a second edition was published. This edition has been extensively revised and updated with new material both in the text and in the form of summary tables. References have been added into the text so that the reader can locate the original literature for further study.

The format and style of the first edition has been retained. It is organized into three sections: (I) Clinical Pharmacology—Describes some of the basic concepts of drug action, clinical significance and use of basic pharmacokinetic principles needed to individualize drug therapy. Individual chapters discuss unique problems in prescribing drugs for the elderly and pediatric populations, and clinically important drug-drug interactions. A new chapter has been added on drug overdose and poisoning.

(II) Therapeutics—Drug therapies of general categories of disease are considered in this section. For example, drug therapies useful for common diseases of the skin, eyes, mouth, cardiovascular, endocrine, respiratory systems and the like are described in individual chapters. A new chapter has also been added to this section on "Diseases of a Tropical Environment." All the chapters in this section have been updated with new material. Several examples of updated material are a more detailed description of PUVA (psoralen plus ultraviolet light-A) therapy for the treatment of psoriasis; coverage of the discovery of a toxin producing *Clostridium difficile* and its possible role in pseudomembranous colitis and antibiotic associated colitis; addition of information on newer antiarrhythmic drugs being introduced into cardiology.

(III) Appendices—There are five excellent sections with tabular data: A—Physiochemical and pharmacokinetic properties of drugs; B—Adverse drug reactions; C—Clinically important drug-drug interactions; D—Selection of antibacterial agents; E—Drug dosage adjustment in renal failure. With the comprehensive and thorough subject index, *Drug Treatment* provides both a rapid access to important drug information, as well as a discussion of drugs from a clinical perspective.

Drug Treatment is a compilation by many internationally recognized experts in clinical medicine and pharmacology. I would enthusiastically recommend this book to medical students, as well as practicing physicians who want more information concerning basic principles of clinical pharmacology and a discussion of therapeutics outside their own specialty.

LARRY WHEELER, PhD
Department of Pharmacology
University of California, Los Angeles
Pharmacy Service, Research Unit
Wadsworth VA Medical Center
Los Angeles

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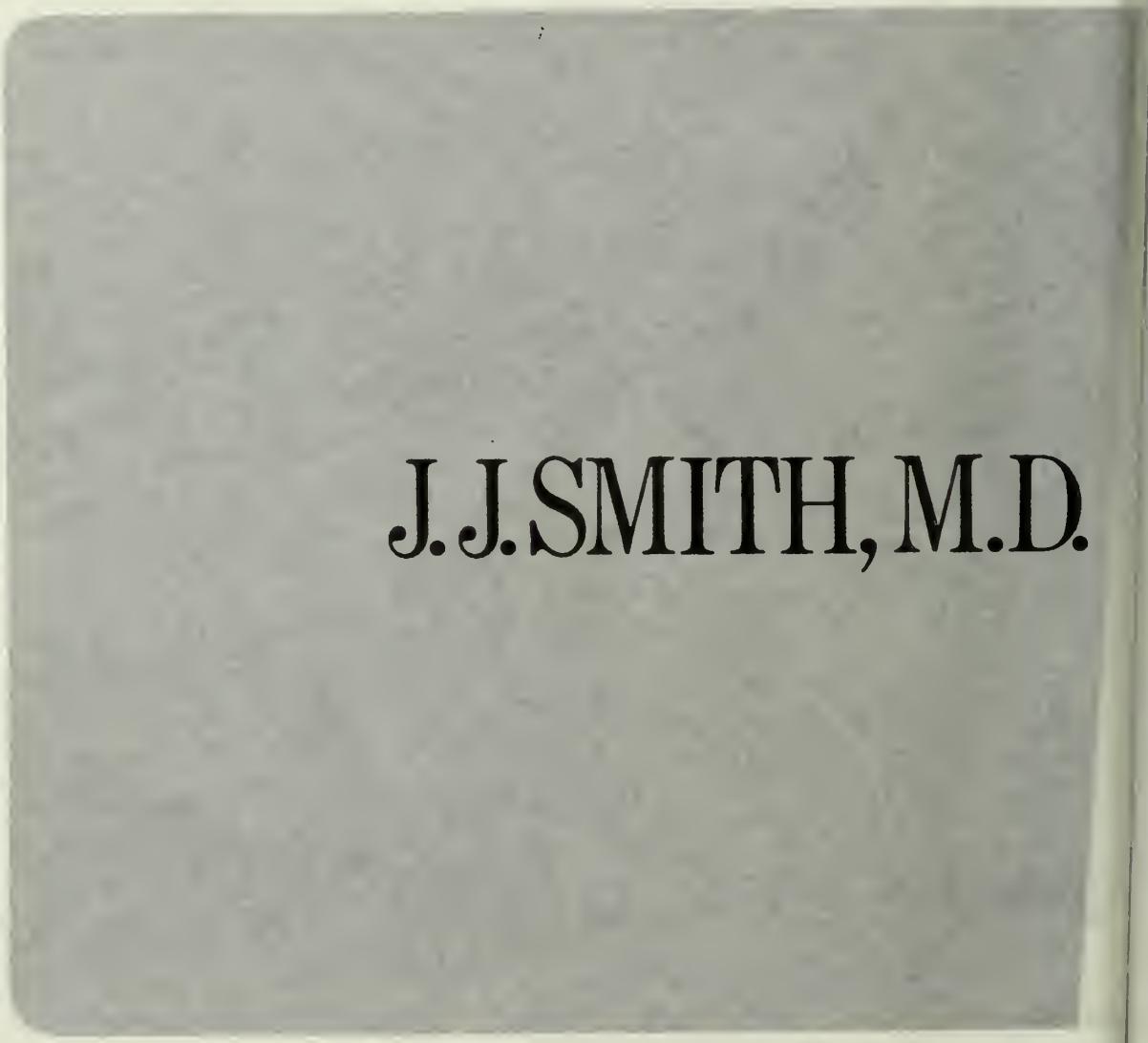

*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her embarrassing sweats and hot flushes. Relieves her discomf Helps her cope.** PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CA

UT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis

There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms

Please see following page for Brief Summary of Prescribing Information.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM

0.625 mg/gm

' PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma – palliative therapy of advanced disease
9. Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion, cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea, increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria, edema, changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism – 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure – 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression) – 1.25 mg daily, cyclically.
3. *Given for a few days.* Prevention of postpartum breast engorgement – 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer – 1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865 – Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 – Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867 – Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. 872 – Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available – Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814/282

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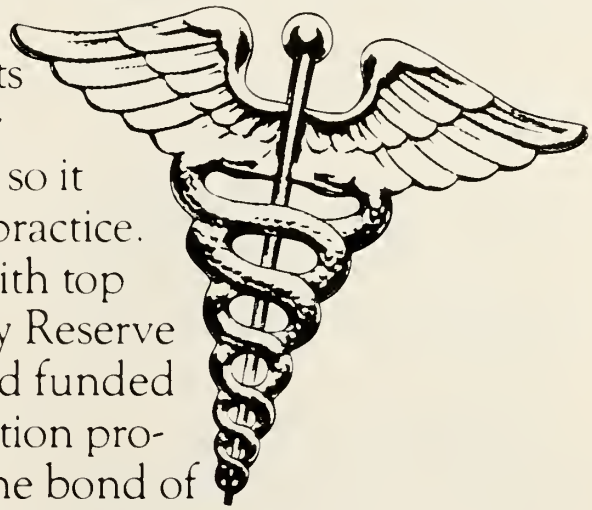

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MAJ James Sheehan, MSC
(714) 836-2866

Idaho, Montana, Oregon and Washington
MAJ Donald T. Cuttie, MSC
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(Continued from Page 29)

Dual-Mode Exercise Testing. International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8651.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Fndn. at Hilton Beach Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 3-5—**Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday-Sunday. 15 hrs.

December 4—**Annual Winter Meeting, Emergency Pediatrics, Part II.** Calif. Chapters, American Academy of Pediatrics, at Holiday Inn on Union Square. San Francisco. Saturday. Contact: Beverly Busher, No. Calif. Chap., AAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Ed., Los Angeles 90024. (213) 825-4617.

December 4—**Total Parenteral Nutrition.** UCLA. Saturday.

December 4-5—**MKSAP VI Review Course.** American College of Physicians and UCLA at UCLA. Saturday-Sunday. 12 hrs. $80. Contact: UCLA.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

December 8—**18th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-10—**MKSAP Review Course.** American College of Physicians and UCD at Hyatt Union Square, San Francisco. Thursday-Friday. Contact: UCD.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

December 10-12—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

IDAHO

See Washington Listings: February 14-18.

MONTANA

September 9-11—**Adult and Pediatric Chest Diseases—Current Views 1982.** Bigfork. Thursday-Saturday. Flathead Lake Lodge. Contact: American Lung Association of Montana, 828 Helena Ave, Helena, MT 59601. (406) 442-6556.

September 30-October 2—**Montana Medical Association Annual Meeting.** Great Falls. Thursday-Saturday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

See also Washington Listings: August 21.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee. New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 27-28—**Pediatric-Adolescent Sports Medicine.** Albuquerque. Friday-Saturday. Hilton Inn. 9 credit hours, also AAFP Prescribed. Contact: Tom Bodnar, Albuquerque & Bernalillo County Medical Association, 303 San Mateo NE, Suite 203, Albuquerque, NM 87108. (505) 268-2446.

September 25—**Margaret E. Prince Lecture on Surgical Aspects of Thyroid and Parathyroid Disease.** Albuquerque. Saturday. Sheraton Old Town. 4 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Elective. Contact: Jonathan Abrams, MD, UNM, School of Medicine. Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

October 8-9—**Diabetes in the Southwest.** Albuquerque. Friday-Saturday. Junior League Building, Old Airport Terminal. 12 credit hours. Also AAFP. Contact: American Diabetes Association, NM Affiliate, 525 San Pedro NE, Albuquerque, NM 87108. (505) 266-5716.

October 9—**Medical and Surgical Management of Cerebrovascular Disease Seminar.** Albuquerque. Saturday. Sheraton Old Town. 7.5 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 14-16—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: NM Heart Institute, 2403 San Mateo NE, Albuquerque, NM 87108. (505) 884-3717.

October 15—**Gynecologic Cancer 1982.** Los Alamos. Friday. Los Alamos Medical Center. 6 credit hours. Contact: James M. Cooper, MD, Los Alamos Council on Cancer, Los Alamos, NM 87544. (505) 662-4412.

November 12-13—**New Mexico Medical Society Interim Meeting.** Las Vegas, New Mexico. Friday-Saturday. Highlands University. 7 credit hours, also AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

February 14-17—**Taos Medical Symposium.** Taos. Monday-Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

February 28-March 4—**Purgatory Ski Symposium.** Durango, Colorado. Monday-Friday. Tamaron Lodge. 20 credit hours, also AAFP. Contact: Gwenn Robinson,MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

acred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

alem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

regon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

egon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

September 10-11—**Ashland Conference: Antimicrobial Therapy in Perspective: The Place of the New Drugs.** Ashland. Friday-Saturday. Ashland Hills Inn. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

(Continued on Page 49)

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PEDIATRICIAN, BOARD ELIGIBLE/CERTIFIED, to join well-established multispecialty group including 4 OB-GYN specialists. Located in the most beautiful part of the San Fernando Valley. Excellent salary depending on experience. Superb, noncontributory retirement, paid malpractice, etc. Partnership available, many other benefits. Write and send CV to Mr. Norman Veis, Administrator, 10660 White Oak, Granada Hills, CA 91344.

OPHTHALMOLOGIST: Over 45, Wanted with interest in Medical Ophth, Peds/Strabismus, Plastics/Orbit or Neuro-Ophth. Dennis Shepard, MD, 1414 E. Main St., Santa Maria, CA 93454. (805) 925-2637.

PHYSICIANS WANTED

IDAHO NEEDS NEUROSURGEON. 20 miles from Boise, near mountains and unlimited recreation. Excellent opportunity, affiliate with 162 bed hospital with rehab. Contact M. Kutsurelis, Assoc. Adm., Mercy Medical Center, 1512 12th Avenue Road, Nampa, ID 83651. Phone (208) 467-1171.

GENERAL SURGEON—needed in established multispecialty clinic in beautiful university town. First year guarantee with full fringe benefits and incentive, new hospital, four season recreation, and ideal family environment. Contact The Budge Clinic, 225 East 4th North, Logan, UT 84321.

ORTHOPEDIST or Medical or Surgical Subspecialist needed for fully equipped small primary care medical group (2 FPs, 2 Gen. Int., 1 Gen. & Vasc. Surg.) in beach orientated Northern California city to complement and complete this busy group. Excellent startup arrangements. 2 good hospitals. Write: H. L. LaFont, MD, Capitola Medical Group, 528 Capitola Ave., Capitola, CA 95010.

GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

RADIOLOGIST to join small group No. California foothill location. Need applicant with post-residency training and/or experience in CT and nuclear cardiology. Box 6305, Western Journal of Medicine, 731 Market St., San Francisco, CA 04103.

ORTHOPEDIC SURGEON—Board Certified with Sports Medicine, arthroscopy and hand training to affiliate with established Orthopedic Surgeon. Office adjacent to well equipped community hospital. Desire personable, mature individual with commitment to patient care. CV and references to Gordon E. Traub, MD, 1275 N. Rose Dr. #130, Placentia, CA 92670.

GENERAL INTERNAL MEDICINE SPECIALIST needed by 36-member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Prefer recent residency trained physicians only. Reply: Mr. D. R. Molesworth, Administrator, or Dr. Daniel Small, 1235 Osos Street, San Luis Obispo, California 93401.

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Harold W. Hartman, Admin. and Chief Operating Officer, Sharp Cabrillo Hospital, 3475 Kenyon Street, San Diego, CA 92110

PHYSICIANS WANTED

AN ACADEMICIAN, family physician, scholar and research leader is sought for a clinical series appointment at either Assistant or Associate Professor level. Applicants should have several publications and a successful record of accomplishment in academic Family Medicine. Clinical teaching, some direct patient care and some research are required. Please send CV to J. Dennis Mull, MD, Dept. of Family Medicine, UCI Medical Center, 101 City Drive South, Orange, CA 92668 by September 30, 1982. An Affirmative Action/Equal Opportunity Employer.

WANTED: ANESTHESIOLOGIST to join three-man group covering 270-bed hospital in Boise, Idaho. No open heart or O.B., CRNA supervision. Salary leading to partnership. Applicant must be U.S. trained and board certified or eligible. Would prefer someone at least three years post residency. References required. Address CV and inquiries to James T. Scanlan, MD, 6560 Emerald, Suite 124, Boise, Idaho 83704.

CALIFORNIA, SAN JOSE: Experienced Emergency Physician wanted to join established group practicing in Emergency Departments at a University affiliated medical center and a community hospital. Fee-for-service compensation, flexible schedules. Send CV or contact: James B. Lane, MD, 1541 The Alameda, Suite A, San Jose, CA 95126. Phone (408) 293-8881.

OPENING FOR PHYSICIAN in Los Angeles office of Surveillance and Utilization Review (SUR) branch, California State Department of Health Services. Full-time position but will consider part-time applicants. Duties involve review of Medi-Cal records to evaluate medical need and appropriateness of services. California license required and ability to travel. Practice experience desirable. Salary up to $5,122 per month plus full benefits. Contact Carolyn Pryor, (213) 620-2751, 107 South Broadway, Room 3110, Los Angeles, CA 90012.

O.R.L.—HEAD AND NECK SURGERY—Mid-sized community in Great Plain state interested in attracting this specialist for our area. You would be part of a young and growing community, regionally oriented, with facilities of modern, fully accredited hospital. Space in medical office building on hospital grounds available. Write: Administrator, Great Plains Medical Center, P.O. Box 1167, 601 West Leota Street, North Platte, Nebraska 69101.

HAWAII—Board certified or eligible gastroenterologist to join 125-physician multispecialty prepaid medical group in Honolulu (Kaiser-Permanente). Excellent fringes. Full malpractice coverage. Salary negotiable. Write: Hawaii Permanente Medical Group, Inc., 1697 Ala Moana Boulevard, Honolulu, HI 96815.
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ORTHOPEDIC SURGEON for busy practice in outstanding So. Cal. area. 34-member multispecialty group seeks full-time board certified specialist to join two other orthopedists. Top-notch opportunity, compensation package and benefits. Send CV to Box 6308, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 48)

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANATOMY OF AN EPIDEMIC—Gordon Thomas and Max Morgan-Witts. Doubleday & Company, Inc., 245 Park Avenue, New York NY 10017, 1982. 366 pages, $16.95.

THE BEGINNING INVESTOR—Edited by Bernard J. Hassan. Medical Economics Books, Box 157, Florence KY 41042, 1982. 131 pages, $9.95* (plus $1.50 handling charge). *Price is subject to change. Contact publisher for correct price after June 1, 1982.

CANCER CHEMOTHERAPEUTIC AGENTS—Handbook of Clinical Data—Second Edition—J. Dennis Preston, PharmD, Clinical Coordinator, Pharmacy Service, VA Medical Center, Assistant Professor, Adjoint Division of Clinical Programs, University of Colorado School of Pharmacy, Denver; Gary H. Lyman, MD, FACP, Associate Professor and Director, Division of Medical Oncology, University of South Florida College of Medicine, Tampa; Charles E. Weber, Jr, PharmD, Chief Pharmacy Service, VA Medical Center, Adjunct Assistant Professor, College of Pharmacy, University of New Mexico, Albuquerque; Mike R. Sather, RPh, MS, Chief, VA Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center, VA Medical Center, Assistant Professor, Department of Pharmacology, College of Pharmacy, University of New Mexico, Albuquerque; and Stephen M. Sleight, RPh, MS, Director, Pharmacy Service, VA Administration Central Office, Washington, DC, and Adjunct Associate Professor, Colege of Pharmacy, University of Kentucky, Lexington. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1982. 263 pages, $21.95.

CLINICAL ETHICS: A Practical Approach to Ethical Decisions in Clinical Medicine—Albert R. Jonsen, PhD; Mark Siegler, MD, and William J. Winslade, PhD, JD. Macmillan Publishing Co., Inc., 866 Third Ave., New York NY 10022, 1982. 187 pages, $15.95.

CLINICAL NUCLEAR MEDICINE—Medical Outline Series—Philip Matin, MD, Associate Clinical Professor of Radiology (Nuclear Medicine), University of California, School of Medicine, Davis, California, and Director, Department of Nuclear Medicine, Roseville Community Hospital, Roseville, California; with 13 contributors. Medical Examination Publishing Co., Inc., 969 Stewart Avenue, Garden City, New York (11530), 1981. 346 pages, $21.50.

COMPARATIVE CORRELATIVE NEUROANATOMY OF THE VERTEBRATE TELENCEPHALON—Edited by Elizabeth C. Crosby, PhD, DSc(Hon), MD-(Hon), and H. N. Schnitzlein, PhD. Macmillan Publishing Co., Inc., 866 Third Ave., New York NY 10022, 1982. 830 pages, illustrated, $75.00.

CURRENT THERAPY 1982—Latest Approved Methods of Treatment for the Practicing Physician—Edited by Howard D. Conn, MD. W. B. Saunders Company, West Washington Square, Philadelphia PA 19105, 1982. 1,016 pages, $38.00.

DIAGNOSTIC BRONCHOSCOPY—Fourth Edition—Peter Stradling, MD-(Lond), FRCP, FRPS. Churchill Livingstone Inc., 19 West 44th Street, New York NY 10036, 1981. 159 pages, 190 illustrations in color, $59.00.

DRUGS IN LITIGATION: Damage Awards Involving Prescription and Nonprescription Drugs—Second Edition—Compiled by the editorial staff of the publishers of LAWYERS' MEDICAL CYCLOPEDIA: Compilation Editors—Richard M. Patterson, JD, Robert E. Robinson, JD; Contributors and Consultants: H. Newcomb Morse, JD, LLM; Charles J. Frankel, MD, LLB, and Monte G. Crumley, PharmB, JD. The Allen Smith Company, 1435 North Meridian St., Indianapolis IN 46202, 1982. 504 pages, $35.00 (softbound).

EMERGENCY MEDICAL THERAPY—Second Edition—Mickey S. Eisenberg, MD, PhD; and Michael K. Copass, MD. W.B. Saunders Company, West Washington Square, Philadelphia, PA (19105), 1982. 407 pages, $16.95.

FOREIGN TRAVEL & IMMUNIZATION GUIDE—Eleventh Edition—Hans H. Neumann, MD. Medical Economics Books, Box 157, Florence KY 41042, 1982. 82 pages, $6.50, plus $1.50 handling charge (paperback).

GETTING BETTER: A MEDICAL STUDENT'S STORY—Kenneth Klein, MD, Fellow in Gastroenterology, Oregon Health Sciences University, Portland. Little, Brown & Company, 34 Beacon Street, Boston, MA (02108), 1981. 284 pages, $12.95.

HOW TO HIRE, TRAIN, AND MANAGE YOUR EMPLOYEES—Edited by Marianne Dekker Mattera. Medical Economics Books, Box 157, Florence KY 41042, 1982. 136 pages, $10.95* (plus $1.50 for handling). *Price is subject to change. Contact publisher for correct price after June 1, 1982.

MAJOR TOPICS IN PEDIATRIC AND ADOLESCENT ONCOLOGY—Edited by Cameron K. Tebbi, MD, Director, Adolescent Unit, Roswell Park Memorial Institute; Consultant in Hematology/Oncology, Children's Hospital of Buffalo, Buffalo, NY. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1982. 361 pages, $39.95.

MEDICAL MICROBIOLOGY—First Edition—Samuel Baron, MD, Chairman, Department of Microbiology, University of Texas Medical Branch, Galveston, Texas, Editor; and Lynn M. Alperin, Associate Editor. Addison-Wesley Publishing Company, Medical/Nursing Division, 2725 Sand Hill Road, Menlo Park, CA (94025), 1982. 952 pages, $29.95.

THE MEDICAL TEACHER—Edited by Kenneth R. Cox, MB, MS, MA, FRCS, FRACS, FACS, and Christine E. Ewan, MB, BS, PhD. Churchill Livingstone Inc., 19 West 44th St., New York NY 10036, 1982. 248 pages, $25.00 (softbound).

NEW BEGINNINGS: COSMETIC SURGERY FOR MEN AND WOMEN—Gloria Heidi and James Earp. Doubleday & Company, Inc., 245 Park Avenue, New York NY 10017, 1982. 304 pages, $19.95.

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN DISEASE): GENETICS, CELL BIOLOGY, AND BIOCHEMISTRY—ADVANCES IN NEUROLOGY—Vol. 29—Vincent M. Riccardi, MD, Robert J. Kleberg Center for Human Genetics, Baylor College of Medicine, Texas Medical Center, Houston, Texas and John J. Mulvihill, MD, Clinical Genetics Section, Clinical Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, Editors; Wanda M. Wade, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, Assistant Editor. Raven Press, 1140 Avenue of the Americas, New York, NY (10036), 1981. 282 pages, no price given.

NUCLEAR MEDICINE IN CLINICAL PRACTICE: Selective Correlation With Ultrasound and Computerized Tomography—Edited by Larry D. Greenfield, MD, and J. Michael Uszler, MD, Verlag Chemie International Inc., Plaza Centre, Suite E, 1020 NW 6th Street, Deerfield Beach, FL (33441), 1982. 410 pages, 202 illustrations, $47.50 (hardbound).

PAIN CONTROL—The Bethesda Program—Bruce Smoller, MD, Assistant Clinical Professor of Psychiatry and Behavioral Science, George Washington University School of Medicine, Washington, DC, and Consultant for Pain Research, National Institutes of Health, Washington, DC; and Brian Schulman, MD, Assistant Clinical Professor of Psychiatry, Georgetown University School of Medicine, Washington, DC, and Consultant to the National Naval Medical Center, Bethesda, Maryland. Doubleday & Company, Inc., 245 Park Ave., New York, NY (10117), 1982. 299 pages, $15.95.

PAEDIATRIC CARDIOLOGY—Volume 3—Edited by Anton E. Becker, Tom G. Losekoot, Carlo Marcelletti, and Robert H. Anderson. Churchill Livingstone Inc., 19 West 44th Street, New York NY 10036, 1981. 485 pages, $65.00.

PRESCRIPTIONS FOR DEATH: THE DRUGGING OF THE THIRD WORLD—Milton Silverman, PhD, University of California, San Francisco School of Medicine, University of California, San Francisco School of Pharmacy, Stanford University School of Medicine; Philip R. Lee, MD, University of California; and Mia Lydecker. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1982. 186 pages, $16.95.

PROTOCOLS FOR HIGH-RISK PREGNANCIES—Edited by John T. Queenan, MD, and John C. Hobbins, MD. Medical Economics Books, Box 157, Florence KY 41042, 1982. 322 pages, $16.95* (plus $1.50 handling charge). *Price is subject to change.

PSYCHOSOCIAL ASPECTS OF NUCLEAR DEVELOPMENTS—Task Force Report 20—Rita R. Rogers, MD, Chairperson, Task Force on Psychosocial Aspects of Nuclear Developments of the American Psychiatric Association; William Beardslee, MD; Doyle I. Carson, MD; Jerome Frank, MD; John Mack, MD; Michael Mufson, MD. American Psychiatric Association, 1700 18th Street, NW, Washington, DC (20009), 1982. 96 pages, $12.00.

PSYCHIATRY 1982—The American Psychiatric Association Annual Review—Edited by Lester Grinspoon, MD. American Psychiatric Association, 1700 Eighteenth Street, NW, Washington DC 20009, 1982. 539 pages, $38.50.

REVIEW OF MEDICAL MICROBIOLOGY—Fifteenth Edition—Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine, Lecturer in Pediatrics, University of California School of Medicine, San Francisco, California; Joseph L. Melnick, PhD, Distinguished Service Professor of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas; and Edward A. Adelberg, PhD, Professor of Human Genetics, Yale University School of Medicine, New Haven, Connecticut. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1982. 553 pages, $17.00.

Rh HEMOLYTIC DISEASE—New Strategy for Eradication—Edited by Fredric David Frigoletto, Jr, MD, Associate Professor of Obstetrics and Gynecology, Harvard Medical School; Chief, Maternal-Fetal Medicine, Boston Hospital for Women; Brigham and Women's Hospital; John Figgis Jewett, MD, Clinical Professor of Obstetrics and Gynecology, Harvard Medical School; Senior Obstetrician and Gynecologist, Boston Hospital for Women, Brigham and Women's Hospital; Angelyn Adele Konugres, PhD, Principal Associate in Obstetrics and Gynecology, Harvard Medical School; Associate Director, Blood Bank, Brigham and Women's Hospital, Boston. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston, MA (02111), 1982. 301 pages, $35.00.

THE SELF SEEKERS—Richard M. Restak, MD. Doubleday & Company, Inc, 245 Park Avenue, New York, NY (10017), 1982. 395 pages, $17.95.

TREATMENT PLANNING IN PSYCHIATRY—Jerry M. Lewis, MD; and Gene Usdin, MD. American Psychiatric Association, 1700 18th Street, NW, Washington, DC (20009), 1982. 433 pages, $27.50.

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UNDER THE INFLUENCE—A Guide to the Myths and Realities of Alcoholism, by James R. Milam and Katherine Ketcham. Madrona Publishers, Inc., 2116 Western Avenue, Seattle, WA 98121, 1981, 210 pages, $12.95.

VITAMINS AND "HEALTH" FOODS: The Great American Hustle, by Victor Herbert, MD, JD, and Stephen Barrett, MD. George F. Stickley Company, 210 West Washington Square, Philadelphia, PA 19106, 1981, 189 pages, $11.95.

(Continued from Page 44)

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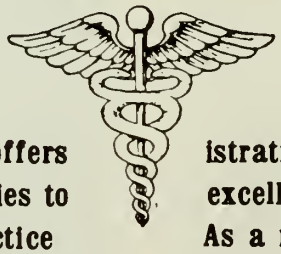

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MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Friday—7:30-8:30 a.m. Contact: Thomas Schwenk, MD, (801) 350-4111.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

(Continued on Page 51)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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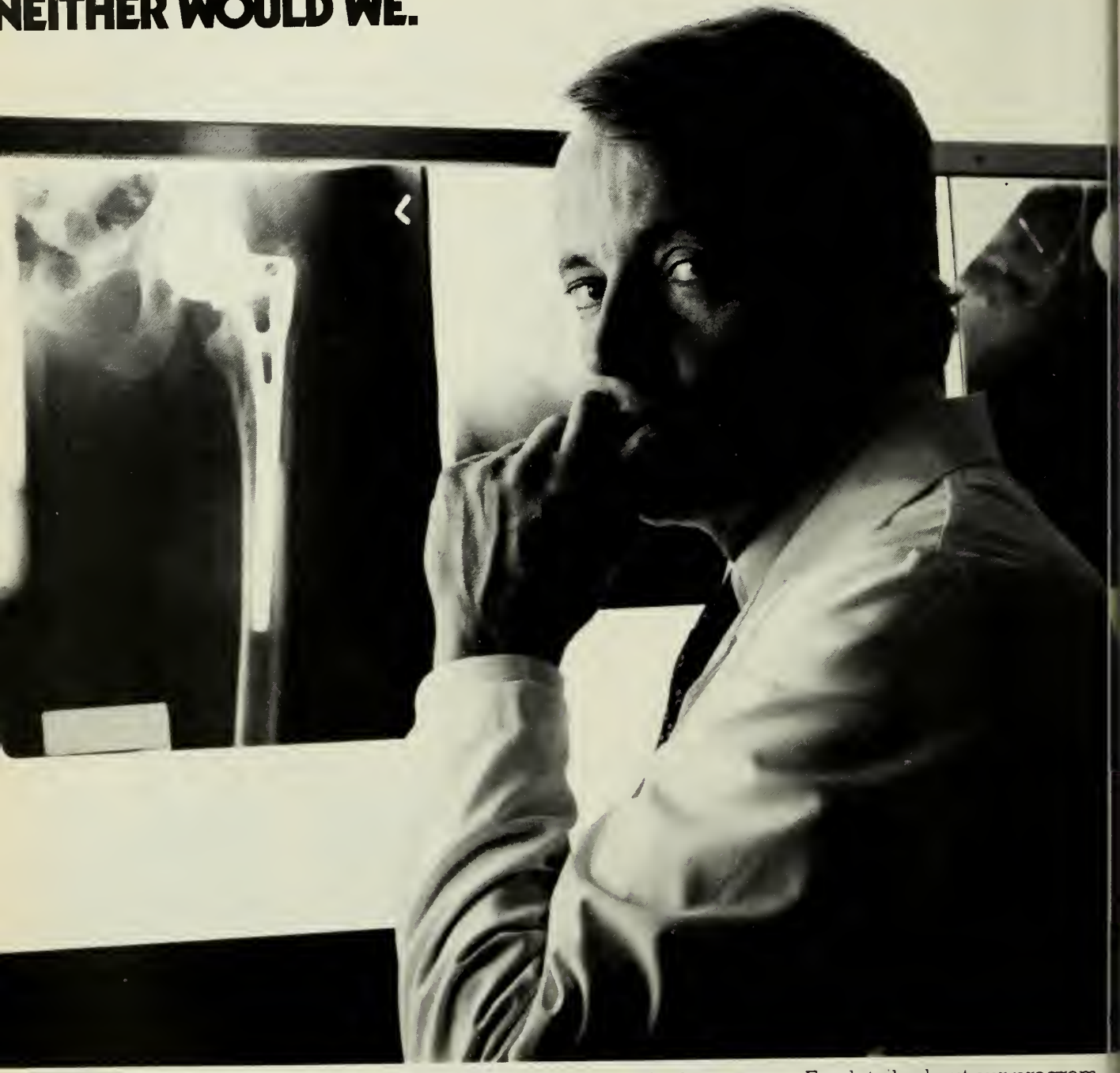

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* * * *

August 19-22—**Ericksonian Psychotherapy and Hypnosis** (Sponsor: University of Utah). Park City. Thursday-Sunday. 24 hrs. Fee: $240. Contact: Lynn Johnson, PhD (801) 261-1412.

September 15-17—**Annual Utah State Medical Association Meeting** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. Fee: To be announced. Credit: To be announced. Contact: Maxcine Fry (801) 355-7477.

September 17—**Pediatric Ophthalmology Meeting: Eye Problems of Children** (Sponsor: University of Utah). Snowbird. Friday. 6 hrs. Fee: $15-$35. Contact: Jane Kivlin, MD (801) 581-6384.

October 6-9—**Child Neurology** (Sponsor: University of Utah). Salt Lake City. Wednesday-Saturday. Hotel Utah. 30 hrs. Fee: To be announced. Contact: Jack Madsen, MD (801) 581-7624.

November 12-13—**New Techniques in Pulmonary Medicine** (Sponsors: LDS Hospital/University of Utah). Salt Lake City. Friday-Saturday. Little America. 10 hrs. $70. Contact: C. Duane Schmidt, MD (801) 353-8201.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

August 16-20—**Advances in Family Practice.** Seattle. Monday-Friday. U/W Health Sciences Building. Contact: U/W.

August 19-21—**(OREGON) Cytology Continuing Education Workshop.** Eugene. Thursday-Saturday. Contact: CME Harborview.

August 21—**(MONTANA) Intensive Conventional Insulin Delivery, and Diabetes in Pregnancy.** Big Sky. Saturday. Contact: Stanlee Dull, Executive Director, American Diabetes Association, Montana Affiliate; Box 2411; Great Falls, MT 59403. (406) 761-0908.

August 27-28—**Urology Update for Primary MDs.** Seattle. Friday-Saturday. U/W South Campus Center. Contact: U/W.

August 29-September 3—**(OREGON) Office Orthopaedics.** Sun River. Sunday-Friday. Sun River Hotel. Contact: U/W.

September 8-15—**13th International Cancer Congress.** Seattle. Wednesday-Wednesday. Seattle Center. Contact: Congress

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

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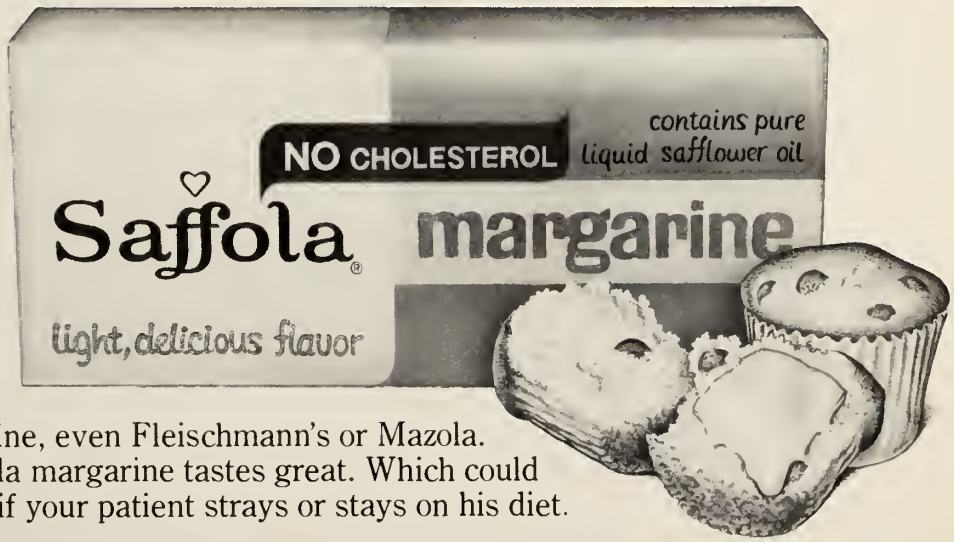

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September 10—**Leonard Memorial Lecture: Endocrine Day.** Seattle. Friday. U/W South Campus Center. Contact: U/W.

September 10-11—**Advanced Cardiac Life Support.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

September 10-11—**Short-term Group Psychotherapy.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

September 16-17—**Plastic Repair and Wound Management.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

September 23-25—**Advances in Internal Medicine.** Seattle. Thursday-Saturday. Westin Hotel. Contact U/W.

September 24—**Pathology Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

September 24-25—**Immediate Care of Sick and Injured.** Seattle. Friday-Saturday. U/W Health Sciences Center. Contact: U/W.

September 30-October 1—**Neuroendrocrinology.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

October 1-2—**Otolaryngology for Non-Otolaryngologists.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

October 8-9—**Annual Cancer Conference: Symptom Management in the Cancer Patient.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 15-16—**The Insulin Pump in Clinical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 21-22—**Nosocomial Infections and Herpes/Hepatitis.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

October 22—**Gynecologic Surgery.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 22-23—**Care and Rehabilitation of the Injured Wrist.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 28-29—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

November 4-5—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 12—**Eye Care in General Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 12-13—**Diabetes. Seattle.** Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

November 13-14—**Medicine and Religion.** Seattle. Saturday-Sunday. U/W Health Sciences Building. Contact: U/W.

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December 3—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 4—**Orthopaedics for Attorneys.** Seattle. Saturday. Sheraton Hotel: Contact: U/W.

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January 20-21—**Cytology.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

January 21-23—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 27-28—**Beta Blockers and Calcium Antagonists.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

January 29-30—**Benefits and Problems of Exercise.** Seattle. Saturday-Sunday. Swedish Hospital. Contact: U/W.

February 3-4—**Ultrasound/Echocardiography.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 14-18—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Friday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 17-18—**Soft Tissue Surgery.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

March 4-5—**High-Risk Infants of the 1980s.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

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(Continued on Page 56)

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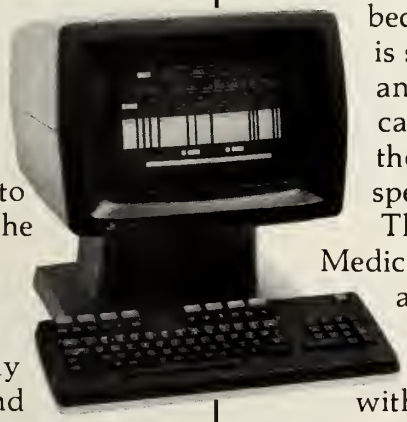

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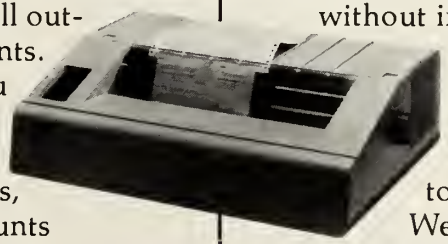

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: May 19-21, 1983, Doubletree Inn, Tucson.

California Medical Association—731 Market St., San Francisco 94103. (415) 777-2000. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. (303) 861-1221. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1983: date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 30-October 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 12-15, 1983, Elko Convention Center, Elko.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 247-0539. Annual Meeting: May 4-6, 1983. Four Seasons Motor Hotel, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Winter Seminar: January 21-22, 1983, Rawlins; Annual Meeting: June 29-July 2, 1983, Jackson Lake Lodge, Moran.

(Continued from Page 53)

May 14—**Sexually Transmitted Diseases in Homosexual Men.** Seattle. Friday. Swedish Hospital. Contact: U/W.

May 19-21—**Office Management of Joint Disease.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

May 26-27—**Clinical Neurogenetics.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

June 2-3—**Managerial Skills.** Seattle. Wednesday-Thursday. Children's Orthopedic Hospital. Contact: U/W.

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June 16-17—**Human Immunogenics.** Seattle. Wednesday-Thursday. Seattle. U/W Health Sciences Building. Contact: U/W.

June 22-24—**Burn.** Seattle. Tuesday-Thursday. Sheraton Hotel. Contact: U/W.

June 27-29—**(OREGON) Office Management of Common Psychiatry Problems.** Sun River. Sunday-Tuesday. Sun River Hotel. Contact: U/W.

June 30-July 1—**(OREGON) Arts and Medicine.** Ashland. Wednesday-Thursday. Southern Oregon State College. Contact: U/W.

July 21-22—**American College of Physicians MKSAP VI.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

July 28-30—**Debates in Otolaryngology.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

August 4-5—**Sports Medicine Summer 1983.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

August 25-26—**Urology for Urologists.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

WYOMING

See Washington listing, September 16-18, 1982.

January 21-22—**Wyoming Medical Society Winter Seminar.** Rawlins. Friday-Saturday. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

June 29-July 2—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

Index to
The Western Journal of Medicine Advertising

ARCO SURGICAL INSTRUMENTS 49
AYERST LABORATORIES
Premarin Tabs/Vag Cream 37, 38, 39, 40
BURROUGHS WELLCOME CO.
Zyloprim 35
CLASSIFIED 44, 48
COOPERATIVE OF AMERICAN PHYSICIANS, THE
Mutual Protection Trust 32
CPS MEDICAL BILLING 45
DelBRON MANAGEMENT SYSTEMS INC. 29
DESERT SPRINGS HOSPITAL OF LAS VEGAS
Symposium—Gastrointestinal Biliary Diseases 47
DOCTORS' CO., THE 50
ELI LILLY AND COMPANY
Ceclor 12
HOSPITAL OF THE GOOD SAMARITAN, THE
Diabetes Symposium 53
HUMANA THE HOSPITAL COMPANY 47
IN-CO COMPANY
Atlantic Medical Center 31
MAUI ELDORADO RESORT 46
MILES PHARMACEUTICALS
Niclocide 20, 21
MITSUBISHI BANK OF CALIFORNIA, THE 5
NATIONAL KIDNEY FOUNDATION OF NORTHERN CALIFORNIA
Advances in Transplantation 2
NEW YORK UNIVERSITY POSTGRADUATE MEDICAL SCHOOL
Symposium—Epidemic Kaposi's Sarcoma and Opportunistic Infections 6
NORCAL MUTUAL INSURANCE CORPORATION 14
PFIZER
Procardia 24, 25, 26, 27, 28
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 13
PRACTICE SERVICE CORPORATION 22
RESEARCH INDUSTRIES INC.
Rimso-50, Rimso-100 33
ROCHE LABORATORIES
Dalmane ..... 2nd cover, 1, 2
Limbitrol ..... 3rd and 4th covers
SMITH KLINE & FRENCH LABORATORIES
Dyazide 34
E. R. SQUIBB & SONS, INC.
Corgard 8, 9, 10
STAFF RESOURCES INC. 46
3M CLINICAL LABORATORY SERVICES 3
UPJOHN CO., THE
Motrin 30
U.S. ARMY RECRUITMENT 48
U.S. ARMY RESERVE 41
WESTERN JOURNAL OF MEDICINE, THE
Subscription 36
WESTLAND MEDICAL SYSTEMS 55
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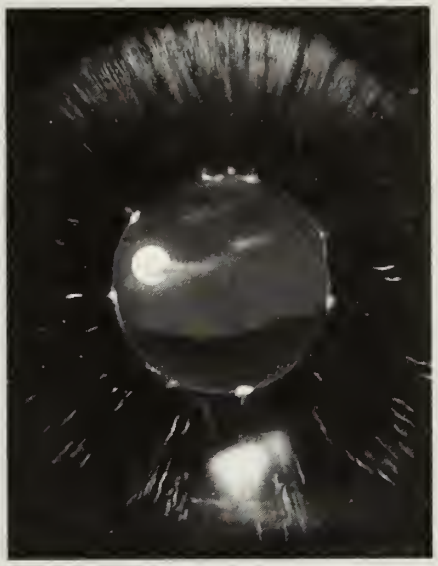

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Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses.
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VOLUME 137 • NUMBER 3 **SEPTEMBER 1982**

ORIGINAL ARTICLES

181 *Anergy in High-Risk Surgical Patients: The Role of Parenteral Nutrition*
DAVID A. SIMONOWITZ, MD; E. PATCHEN DELLINGER, MD; MICHAEL R. ORESKOVICH, MD; JOSEPH C. STOTHERT, MD, and WILLIAM A. EDWARDS, RPh

186 *Hemoglobin E in Indochinese Refugees* THOMAS M. CUNNINGHAM, MD

191 *Hot Tub Folliculitis: A Clinical Syndome* BARRY J. ZACHERLE, MD, and DIANE S. SILVER, MD

MEDICAL PROGRESS

195 *Mast Cells in Allergic Diseases and Mastocytosis*
DIANA L. MARQUARDT, MD, and STEPHEN I. WASSERMAN, MD

SPECIALTY CONFERENCE

213 *Recent Developments in the Diagnosis and Treatment of Urinary Tract Infections*
Discussant: WALTER E. STAMM, MD

CLINICOPATHOLOGIC CONFERENCE

221 *Rash and Eosinophilia in a 23-Year-Old Man*
Discussants: RAY BACHHUBER, MD; JOHN H. FITCHEN, MD, and BARBARA HARTY-GOLDER, MD

EPITOMES OF PROGRESS

228 *Otolaryngology/Head and Neck Surgery—Important Advances in Clinical Medicine*

EDITORIALS

234 • *The Payors' Revolt* • *Mast Cells and Homeostasis: Another View* • *Paranoia and Nuclear Armaments* • *In Defense of the Bladder* • *The Enigma of the Eosinophil*

CASE REPORTS

241 *Bilious Ascites Simulating Tuberculous Peritonitis*
DENNIS L. AVNER, MD; HANS C. WEST, MD, and LAYTON F. RIKKERS, MD

243 Campylobacter *Colitis—A Cause of Chronic Diarrhea in Children*
MELVIN B. HEYMAN, MD, MPH; VICTORIA I. PATERNO, MD, and MARVIN E. AMENT, MD

245 *Transient Bifascicular Block Following Blunt Chest Trauma*
KENNETH W. CARR, MD; ALLEN D. JOHNSON, MD, and GABRIEL GREGORATOS, MD

CORRESPONDENCE

250 • *The Ash Babies Never Came* • *Pacilepsy* • *Acronyms in Medical Papers* • *Comments on Ethical Protocol*

TOPICS IN PRIMARY CARE MEDICINE

253 *The Evaluation of Anemia* STEPHEN J. McPHEE, MD

HISTORY OF MEDICINE

258 *The Foul Tongue: A 19th Century Index of Disease* JOHN S. HALLER, Jr, PhD

INFORMATION

265 *Treatment of Impaired Physicians/The California Board of Medical Quality Assurance Program*
ROBERT LARSEN, MD

269 *Diabetic Retinopathy* LEROY W. VAUGHN, MD

271 *In Memoriam*

Medical Practice Questions, See Pages 194 and 257

Detailed Table of Contents, See Advertising Pages 7 and 11

Information for Authors, See August Issue, Advertising Page 54

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Because uropathogens on vaginal cells...

New *in vitro* studies indicate specific *E.coli* receptors on the urogenital epithelium may be an important factor in recurrent infection.

Researchers have recently identified a chemical receptor for *E. coli* on the uroepithelial cells of women who are subject to recurrent urinary tract infections.[1]

The receptor is a glycosphingolipid known as α-D-Gal*p* (1→4)-β-D-Gal*p*. This carbohydrate is an antigen found on the red blood cells and the uroepithelial cells of women who have P-positive phenotypes.[1,2] It is *not* present on the erythrocytes or uroepithelial cells of women who are P-negative. Women who belong to the rare P-negative blood group had a much lower capacity for binding uropathogenic *E. coli* to their urogenital cells *in vitro* and had never experienced recurrent urinary tract infection. The cells from P-positive women, on the other hand, had a very high capacity for binding virulent *E. coli.* These women are generally much more likely to get recurrent infections. The chemical receptor appears to be a major factor responsible for this.[1]

Adherence of *E.coli* to vaginal mucosal cells increases susceptibility to urinary infections.

Another study, comparing women who experienced three or more urinary tract infections per year with healthy controls, found that vaginal cells from the women with recurrent urinary infections had a greater tendency to bind *E. coli in vitro*—even when the cells were cultured while there was no infection. The researchers speculated that deficient host defense mechanisms in vaginal mucosal cells may be responsible for recurrent urinary infections in many women.[3] *E. coli* and other uropathogens may colonize the vaginal introitus, adhere to receptors on mucosal cells and then infect the urinary tract.

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*Due to susceptible organisms such as *E. coli, Klebsiella-Enterobacter* and *Proteus* species.

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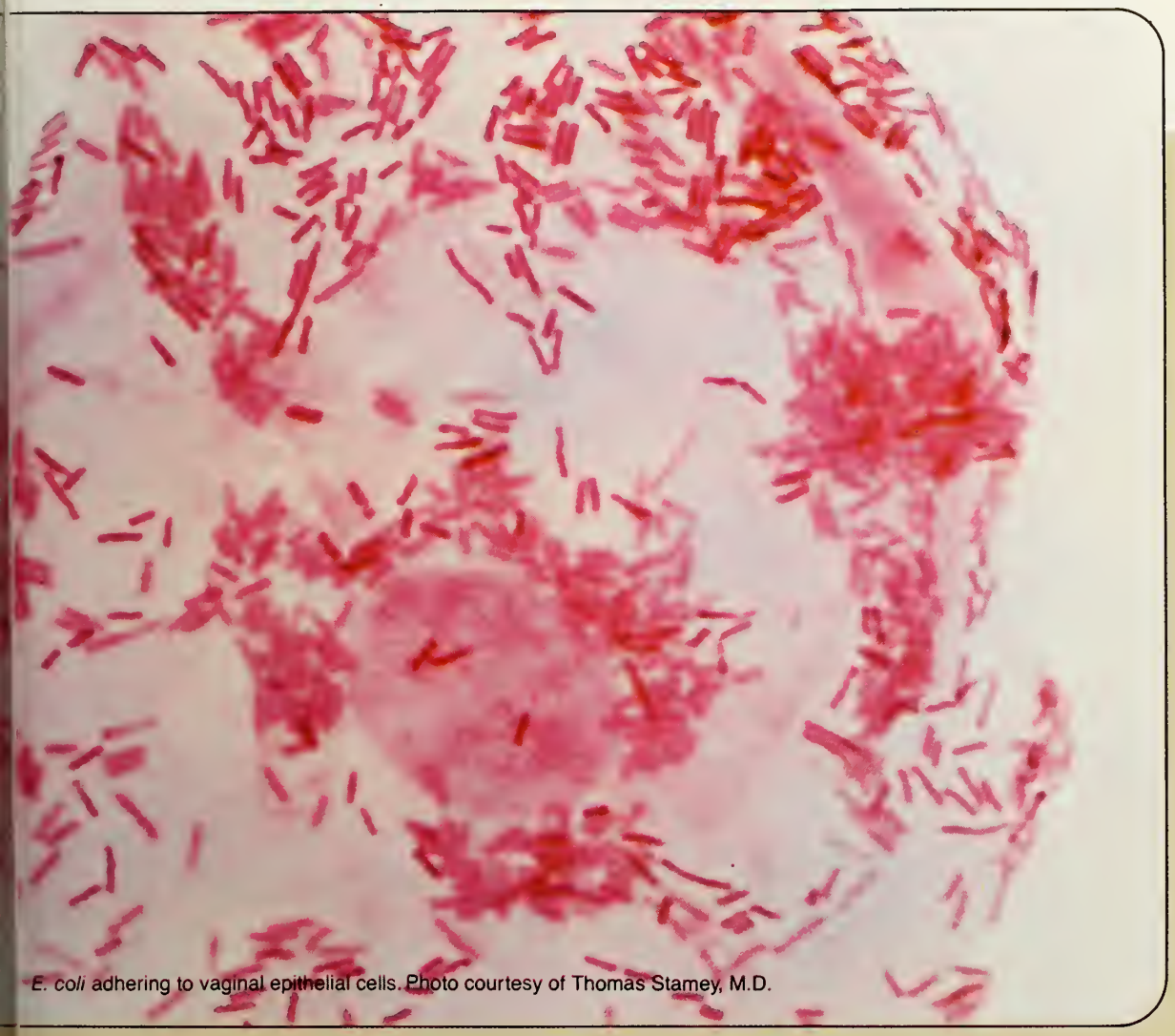

E. coli adhering to vaginal epithelial cells. Photo courtesy of Thomas Stamey, M.D.

The pharmacologic and pharmacokinetic activities of Bactrim (trimethoprim and sulfamethoxazole/Roche) make it particularly appropriate for the treatment of recurrent urinary infections.* The vast majority of *E. coli* strains and a wide spectrum of other common uropathogens are susceptible to Bactrim *in vitro*.[4] Bactrim achieves high concentrations in the urine, and the trimethoprim component diffuses into the vaginal area and attacks susceptible uropathogens that cling to mucosal cells.[5] In the fecal flora, Bactrim suppresses Enterobacteriaceae,[6] with little resulting emergence of resistant organisms. Bactrim is contraindicated in pregnancy at term, nursing mothers, infants under two months of age and documented megaloblastic anemia due to folate deficiency.

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References: 1. Källenius G *et al: Lancet 2*:604-606, Sep 19, 1981. **2.** Lomberg H *et al: Lancet 1*:551-552, Mar 7, 1981. **3.** Schaeffer AJ *et al: N Engl J Med 304*:1062-1066, Apr 30, 1981. **4.** BacData Medical Information Systems: *Antibiotic Sensitivity Report*, Winter Series, 1981. **5.** Stamey TA, Condy M: *J Infect Dis 131*:261-266, Mar 1975. **6.** Rubin RH, Swartz MN: *N Engl J Med 303*:426-431, Aug 21, 1980.

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Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment. Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

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THE WESTERN
Journal of Medicine

VOLUME 137 • NUMBER 3 **SEPTEMBER 1982**

TABLE OF CONTENTS

ORIGINAL ARTICLES

181 *Anergy in High-Risk Surgical Patients: The Role of Parenteral Nutrition*
DAVID A. SIMONOWITZ, MD; E. PATCHEN DELLINGER, MD; MICHAEL R. ORESKOVICH, MD; JOSEPH C. STOTHERT, MD, and WILLIAM A. EDWARDS, RPh
From the Departments of Surgery and Pharmacy and the Nutritional Support Service, University of Washington School of Medicine, Harborview Medical Center, Seattle.

186 *Hemoglobin E in Indochinese Refugees* THOMAS M. CUNNINGHAM, MD
From the Department of Internal Medicine, St. Mary's Hospital and Medical Center, San Francisco. Dr. Cunningham is now in private practice in Sebastopol, California.

191 *Hot Tub Folliculitis: A Clinical Syndome* BARRY J. ZACHERLE, MD, and DIANE S. SILVER, MD
Drs. Zacherle and Silver are in private practice in Napa, California.

MEDICAL PROGRESS

195 *Mast Cells in Allergic Diseases and Mastocytosis*
DIANA L. MARQUARDT, MD, and STEPHEN I. WASSERMAN, MD
From the Division of Rheumatic Diseases/Allergy, Department of Medicine, School of Medicine, University Hospital, University of California Medical Center, San Diego.

SPECIALTY CONFERENCE

213 *Recent Developments in the Diagnosis and Treatment of Urinary Tract Infections*
Discussant: WALTER E. STAMM, MD
From a weekly Grand Rounds in the Department of Medicine, University of Washington, Seattle. The transcript was edited by Drs. Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor and Chairman of the Department of Medicine.

CLINICOPATHOLOGIC CONFERENCE

221 *Rash and Eosinophilia in a 23-Year-Old Man*
Discussants: RAY BACHHUBER, MD; JOHN H. FITCHEN, MD, and BARBARA HARTY-GOLDER, MD
From the Department of Medicine, The Oregon Health Sciences University, Portland. The transcript was edited by George A. Porter, MD, Professor and Chairman of the Department of Medicine.

EPITOMES OF PROGRESS

Otolaryngology/Head and Neck Surgery—Important Advances in Clinical Medicine
Items of progress in otolaryngology/head and neck surgery. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

228 *Snoring* F. BLAIR SIMMONS, MD

228 *Carotid Artery Management in a Radical Surgical Procedure of the Neck*
STANLEY W. COULTHARD, MD

229 *Carbon Dioxide Lasers in Managing Basal Skull Tumors*
MANSFIELD F. W. SMITH, MD; RAYMOND L. LAGGER, MD, and JOHN B. SHINN, MD

229 *Surgical Speech Rehabilitation After Total Laryngectomy* B. W. JAFEK, MD, and J. D. WHITE, MD

230 *New Treatment for Fractures of Edentulous Mandibles* PAUL A. LEVINE, MD

230 *Surgical Procedure for Progressive or Fluctuant Sensorineural Hearing Loss in Children*
N. R. T. PASHLEY, MB, BS, FRCS(C)

231 *Cineradiography in the Evaluation of Obstructive Sleep Apnea* CHARLES F. KOOPMANN, Jr, MD

231 *The Treatment of Rhinitis With Topically Administered Steroids*
J. E. ARNOLD, MD, and J. W. KOLMER, MD

232 *Digital Subtraction Videoangiography* ROGER W. MILLER, MD

232 *Recent Advances in the Treatment of Serous Otitis Media*
D. V. BARCZ, MD, and B. W. JAFEK, MD

(Continued on Page 11)

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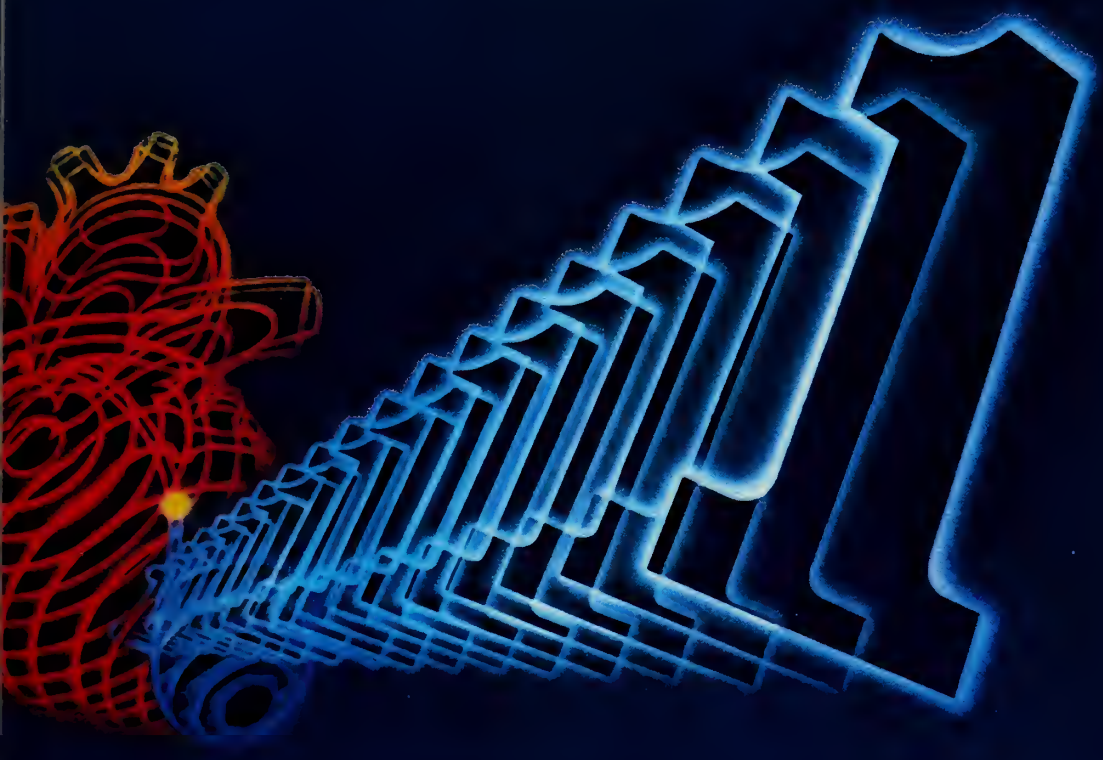

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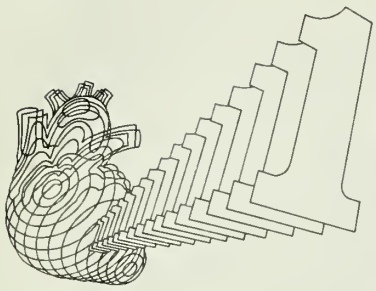

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WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets. The 40 mg and 80 mg tablets are also available in convenience packages containing 4 blister cards of 7 tablets each.

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(Continued from Page 7)

EDITORIALS

234 *The Payors' Revolt*

234 *Mast Cells and Homeostasis: Another View* ROBERT A. LEWIS, MD
From the Department of Medicine, Harvard Medical School, Boston.

236 *Paranoia and Nuclear Armaments*

237 *In Defense of the Bladder* CALVIN M. KUNIN, MD
Dr. Kunin is Professor and Chairman of the Department of Medicine, The Ohio State University, Columbus.

239 *The Enigma of the Eosinophil* PAUL B. BEESON, MD
Dr. Beeson is Professor of Medicine, University of Washington School of Medicine, Seattle.

CASE REPORTS

241 *Bilious Ascites Simulating Tuberculous Peritonitis*
DENNIS L. AVNER, MD; HANS C. WEST, MD, and LAYTON F. RIKKERS, MD
From the Departments of Medicine and Surgery, University of Utah Medical Center and the Veterans Administration Medical Center, Salt Lake City.

243 Campylobacter *Colitis—A Cause of Chronic Diarrhea in Children*
MELVIN B. HEYMAN, MD, MPH; VICTORIA I. PATERNO, MD, and MARVIN E. AMENT, MD
From the Department of Pediatrics, UCLA School of Medicine. Dr. Heyman is now affiliated with the Department of Pediatrics, Gastroenterology Unit, University of California, San Francisco.

245 *Transient Bifascicular Block Following Blunt Chest Trauma*
KENNETH W. CARR, MD; ALLEN D. JOHNSON, MD, and GABRIEL GREGORATOS, MD
From the Division of Cardiology, Veterans Administration Medical Center and the University of California Medical Center, San Diego.

CORRESPONDENCE

250 *The Ash Babies Never Came* PATRICIA STARZYK, PhD, and FLOYD FROST, PhD

250 *Pacilepsy* MARTIN TERPLAN, MD

251 *Acronyms in Medical Papers* ALFRED G. ROBINSON, MD

Comments on Ethical Protocol

251 MARVIN J. SHAPIRO, MD

251 JOHN M. GOLDENRING, MD, MPH

252 HUGH A. FRANK, MD

TOPICS IN PRIMARY CARE MEDICINE

253 *The Evaluation of Anemia* STEPHEN J. McPHEE, MD
From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

HISTORY OF MEDICINE

258 *The Foul Tongue: A 19th Century Index of Disease* JOHN S. HALLER, Jr, PhD
Dr. Haller is Professor of History and Associate Vice President for Academic Affairs—Instructional Programs, California State University, Long Beach, California.

INFORMATION

265 *Treatment of Impaired Physicians/The California Board of Medical Quality Assurance Program*
ROBERT LARSEN, MD
From the Department of Psychiatry, University of California, San Francisco, School of Medicine.

269 *Diabetic Retinopathy* LEROY W. VAUGHN, MD
Dr. Vaughn is Assistant Professor, Jules Stein Institute, UCLA School of Medicine; Director, Retina Service, Martin Luther King, Jr, General Hospital, Los Angeles, and affiliated with the Diabetic Eye Consultants Medical Group, Inc., Inglewood, California, and the Diabetes Center, Los Angeles.

271 *In Memoriam*

Medical Practice Questions, See Pages 194 and 257

Announcement of the 93rd Annual Meeting of the Washington State Medical Association, Yakima, October 7-10, 1982, See Advertising Pages 46 and 47

Information for Authors, See August Issue, Advertising Page 54

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 12)

★★ Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society

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September 16-18—**4th Postgraduate Course in Medical Mycology (Dermatomycology).** UCSF. Thursday-Saturday.

September 20-22—**Alcoholism Treatment, Cooperation or Competition.** Scripps Memorial Hospital at Vacation Village, San Diego. Monday-Wednesday. $190. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

September 20-24—**7th Annual Hawaiian Seminar on Clinical Anesthesiology.** Calif. Society of Anesthesiologists at Marriott, Maui. Monday-Friday. 21 hrs. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

September 21-22—**American Heart Association-Greater Los Angeles Affiliate—50th Anniversary Fall Symposium.** Hilton, Los Angeles. Tuesday-Wednesday. 11 hrs. $70. Contact: Marilyn Cowan, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

September 24—**Advances in Transplantation—15th Annual Symposium on Renal Disease.** National Kidney Foundation of No. Calif. at Stanford. Friday. 6 hrs. $80. Contact: Nat'l Kidney Fndn. of No. Calif., 856 Stanton Rd, Burlingame 94010. (415) 697-0110.

September 24-25—**Toxicology for Occupational Health Personnel.** PMC at Miyako Hotel, San Francisco. Friday-Saturday.

September 24-25—**Antigens and Immunotherapy: Present and Future.** Los Angeles and California Societies of Allergy and Clinical Immunology at Marriott, Newport Beach. Friday-Saturday. Contact: Warren Richards, MD, Allergy-Clinical Immunology Div., Childrens Hosp., P.O. Box 54700, Terminal Annex, Los Angeles 90054.

September 24-25—**Update in Internal Medicine—27th Annual Medical Symposium.** So. Calif. Permanente Medical Group and Kaiser Fndn. Hospitals at Century Plaza, Los Angeles. Friday-Saturday. Contact: Mark Anthony, SCPMG, Regional Dept. of Ed. and Research, 4747 Sunset Blvd., Los Angeles 90027. (213) 667-4241.

September 24-25—**Sexual Issues in Medical Office Practice.** UCSF. Friday-Saturday. 10½ hrs. $125. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

September 24-26—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

September 25—**Cancer and the Environment.** San Francisco Regional Cancer Fndn.; French Hosp. Med. Ctr.; Am. Cancer Soc., S.F. Unit, at French Hospital, San Francisco. Saturday. 4 hrs. Contact: Cecilia Cotter, S.F. Reg. Cancer Fndn., Bldg. 1805, San Francisco 94129. (415) 221-2132.

September 25—**Do's and Don'ts With Diets and Drugs.** UCLA. Saturday. 7 hrs. $90.

September 25—**What's New in Infectious Diseases.** Hospital of the Good Samaritan at Le Baron Hotel, San Jose. Saturday. 7 hrs. $40. Contact: Janice Grogan, Med. Ed., Hosp. of the Good Samaritan, 2425 Samaritan Dr., San Jose 95124. (408) 559-2457.

September 25—**Clinical Ultrasound in Obstetrics and the Neonatal Period.** Sacramento Radiology Research and Education Fndn. and No. Calif. Radiological Soc. at Sacramento. Saturday. 6 hrs. $75. Contact: J. P. McGahan, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

September 25-October 3—**2nd Annual Recognition and Management of Diving Casualties.** UCSD at Sheraton Island Marina Inn, San Diego. 9 days. 60 hrs. Contact: Shirley Kolkey, Medicine, Education and Research Fndn., P.O. Box 81344, San Diego 92138.

September 28-October 1—**American College of Emergency Physicians.** San Francisco. Tuesday-Friday. Contact: Registrar, ACEP, P.O. Box 61911, Dallas 75261. (214) 659-0911.

(Continued on Page 14)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059 (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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(Continued from Page 12)

September 29-30—**39th Annual Brennemann Memorial Lectures.** L.A. Pediatric Soc. at Hilton, Los Angeles. Wednesday-Thursday. 11 hrs. $145, members; $175, nonmembers. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 29-October 1—**New Concepts in Maxillofacial Surgery.** STAN and Swiss Assn. for the Study of Internal Fixation at Stanford. Wednesday-Friday. 17 hrs. $400. Contact: ASIF Course Secretariat, P.O. Box 514, Wayne, PA 19087. (215) 293-0654.

September 29-October 2—**Reconstructive Surgery of the Shoulder, Elbow, Hip and Knee: An In-Depth Course and Workshop.** UCLA. Wednesday-Saturday. 30 hrs. $450.

September 29-October 3—**Physical Fitness Seminar '82.** LLU at Canyon Hotel, Palm Springs. Wednesday-Sunday. 13 hrs. Contact: Alumni Assn., LLU Sch. of Med., 11245 Anderson St., Suite 200, Loma Linda 92354. (714) 824-4633.

September 30-October 2—**Postgraduate Institute on Geriatrics.** CMA at Hotel del Coronado, Coronado. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

September 30-October 2—**Pulmonary Update.** UCSF. Thursday-Saturday.

October 1-2—**Advances in Heart Disease, Aging, Diabetes and Cancer Research.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. Contact: Robert J. Morin, MD, Harbor-UCLA Medical Ctr., Torrance 90509. (213) 533-2233.

October 1-2—**Frontiers in Medicine: Implications for the Future.** UCLA at Beverly Hilton, Beverly Hills. Friday-Saturday. 16 hrs. $225.

October 1-2—**Intraocular Lens Workshop.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $500. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 1-2—**Mycology Review.** STAN. Friday-Saturday. 14 hrs. Contact: Paul H. Jacobs, MD, Dermatology Dept., Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-7813.

October 1-2—**Pediatrics With Sydney Gellis.** UCD at Red Lion Inn, Sacramento. Friday-Saturday. 10 hrs. $95.

October 1-3—**Ambulatory Electrocardiography: Clinical Applications, Methodology and Interpretation.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 1-3—**Recent Advances in Anesthesia.** Anesthesiology Educational Fndn. at Holiday Inn, Monterey. Friday-Sunday. 10½ hrs. $200. Contact: AEF, P.O. Box 24230, Federal Bldg., Los Angeles 90024.

October 2—**Flexible Fiberoptic Sigmoidoscopy, II.** Herrick Hospital and Health Center at Holiday Inn, Emeryville. Saturday. 7 hrs. $100. Contact: Lloyd C. Patterson, MD, Dir. of Med. Ed., Herrick Hosp. and Health Ctr., 2001 Dwight Way, Berkeley 94704. (415) 540-4546.

October 2—**5th Annual Heart Symposium.** Northridge Hospital Medical Center at Century Plaza, Los Angeles. Saturday. Contact: Sandra Rozzen, Northridge Hosp. Med. Ctr., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

October 2—**Gynecology Oncology Conference.** Sutter Community Hospitals at Hotel El Rancho, Sacramento. Saturday. 7 hrs. Contact: Gail Catlin, Oncology Coordinator, Sutter Mem. Hosp., 52nd and F Sts., Sacramento 94819. (916) 454-3333, ext. 1298.

October 2—**TMJ: What Is It and What To Do About It.** Scripps Clinic and Research Fndn. at Hilton, San Diego. Saturday. 6 hrs. $90. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 2-3—**The Skin from A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Saturday-Sunday.

October 3-6—**Controversies and Recent Advances in Pulmonary Medicine.** UCSF at Ahwahnee Hotel, Yosemite. Sunday-Wednesday. 17 hrs. $225. Contact: Karen L. Dutkowski, UCSF, Fresno-Central San Joaquin Valley Med. Ed. Prog., 2615 E. Clinton, Fresno 93703. (209) 224-3235.

October 4-7—**American Academy of Family Physicians—1982 Scientific Assembly.** Moscone Center, San Francisco. Monday-Thursday. 30+ hrs. $50, members; $75, nonmembers. Contact: Edward E. Daleske, Committee on Sci. Prog., AAFP, 1740 W. 92nd St., Kansas City, MO 64114. (816) 333-9700.

October 4-7—**Practical Electrocardiography—ECG Course for Primary Physicians.** Memorial Hospital Medical Center of Long Beach at Caesar's Palace, Las Vegas. Monday-Thursday. 14 hrs. $225. Contact: Asst. Dir., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 4-9—**Review Course in Obstetrics and Gynecology and Gynecological Histopathology.** Memorial Hospital Medical Center of Long Beach at Sheraton Newport, Newport Beach. Monday-Saturday. 48 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 6-10—**American Academy for Cerebral Palsy and Developmental Medicine—36th Annual Meeting.** Sheraton Harbor Island, San Diego. Wednesday-Sunday. 26 hrs. Contact: Kevin Johns, Convention Mgr., P.O. Box 11083, Richmond, VA 23230. (804) 355-9529.

October 7-8—**52nd Annual Physicians' Postgraduate Symposium on Cardiovascular Diseases.** American Heart Assn., San Francisco Chap., at San Franciscan Hotel, San Francisco. Thursday-Friday. 11 hrs. Contact: Ms. Kari Olila, AHA, S.F. Chap., 421 Powell St., San Francisco 94102. (415) 433-2273.

October 7-9—**CT of the Lumbar Spine.** UCSF at Fairmont Hotel, San Francisco. Thursday-Saturday. $275.

October 7-10—**Society of Nuclear Medicine—7th Annual Western Regional Meeting.** Town and Country, San Diego. Thursday-Sunday. Contact: Jean Parker, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 7-10—**Western Dialysis and Transplant Society—13th Annual Meeting.** Sahara Hotel, Las Vegas. Thursday-Sunday. 12 hrs. $150. Contact: Linda Huprich, 1181 S. Los Robles, Pasadena 91106.

October 8-10—**Pacific Occupational Safety and Health Conference.** No. Calif. Sections, Am. Industrial Hygiene Assn., Am. Soc. of Safety Engineers, Health Physics Soc.; Calif. Soc. of Industrial Med. and Surg.; Western Assn. of Occupational Health Nurses; and Mt. Zion Hosp. and Med. Ctr. at Marriott's Great America, Santa Clara. Friday-Sunday. 14 hrs. Contact: Annette Haag, RN, Fireman's Fund Insurance, 1600 Los Gamos Dr., San Rafael 94911. (415) 492-7758.

October 9—**Pediatric Ophthalmology for the Primary Care Practitioner.** Memorial Hosp. Medical Ctr.-UCI Ctr. for Health Education, Long Beach. Saturday. 6 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 9-10—**Update on Bone and Calcium.** UCSF. Saturday-Sunday.

October 9-10—**Sexual Deviation: Contemporary Psychoanalytic Views.** So. Calif. Psychoanalytic Soc. at Beverly Hilton, Beverly Hills. Saturday-Sunday. Contact: Mrs. Carol Ziff, Exec. Sec., SCPS, 9024 Olympic Blvd., Beverly Hills 90211. (213) 936-2877.

October 9-16—**Gastroenterology.** USC at Mauna Kea Beach Hotel, Kamuela. One week. 29 hrs.

October 9-17—**7th Annual International Body Imaging Conference.** West Park Hospital at Sheraton Royal Waikoloa Hotel, Kona, Hawaii. One week. 28 hrs. $385. Contact: Conf. Sec., Dept. of Radiology, West Park Hosp., 22141 Roscoe Blvd., Canoga Park 91304. (213) 340-0580, ext. 280.

(Continued on Page 16)

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(Continued from Page 14)

October 10-15—**American Physiological Society—33rd Annual Fall Meeting.** Town and Country, San Diego. Sunday-Friday. 30 hrs. Contact: Geri Goodenough, Office of Sci. Mtgs., APS, 9650 Rockville Pike, Bethesda, MD 20814. (301) 530-7010.

October 10-15—**Annual Meeting of American Society of Plastic and Reconstructive Surgeons, Plastic Surgery Educational Foundation, and American Society of Maxillofacial Surgeons.** Sheraton Waikiki, Honolulu. Sunday-Friday. Contact: Linda Campbell, Mtg. Dept., ASPRS, 233 N. Michigan Ave., Suite 1900, Chicago 60601. (312) 856-1818.

October 10-15—**Reproductive Health Care: Changing Concepts in Fertility Regulation.** Wayne State Univ. at Marriott, Maui. Sunday-Friday. Contact: E. S. E. Hafez, Dept. of Obstetrics/Gynecology, Wayne State Univ. Sch. of Med., Med. Research Bldg., Rm. 416, 5500 E. Canfield, Detroit 48201. (313) 577-1011.

October 11-13—**6th Annual Cancer Symposium.** Scripps Memorial Hosp. at Vacation Village, San Diego. Monday-Wednesday. $300. Contact: Nomi Feldman, 3770 Tansy, San Diego 92121. (714) 453-6222.

October 11-14—**Hawaii Medical Association—126th Annual Scientific Meeting.** Hilton Hawaiian Village, Honolulu. Monday-Thursday. Contact: Irene Wong, Mtg. Coordinator, HMA, 320 Ward Ave., Honolulu 96814. (808) 536-7702.

October 11-15—**Emergency Medicine.** USC. Monday-Friday.

October 11-15—**Postgraduate Institute for Emergency Room Physicians—Symposium III.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

October 11-15—**12th Annual Review Course in Gynecology and Obstetrics.** USC at Hilton, Pasadena. Monday-Friday. 35 hrs. $450.

October 13—**Post-Operative Complications—Their Prevention and Management.** LLU. Wednesday. 4 hrs.

October 13—**12th Annual Respiratory Medicine Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

October 14-16—**Western Society of Allergy and Immunology—21st Annual Scientific Session.** Hyatt at Union Square, San Francisco. Thursday-Saturday. Contact: Joyce M. Gullixson, Exec. Sec., 1700 S.W. Columbia, Portland 97201. (503) 224-6159.

October 14-16—**Non-Invasive Diagnostic Cardiology and Electrophysiology.** Foundation for Cardiovascular Research and American Heart Association's Council on Clinical Cardiology at Stanford Court, San Francisco. Thursday-Saturday. 17 hrs. Contact: Fndn. for Cardiovascular Research, 201 N. El Molino, Suite 100, Pasadena 91101. (213) 792-4173.

October 14-16—**Workshops in Clinical Hypnosis.** UCSD at Hanalei Hotel, San Diego. Thursday-Saturday. 21 hours. $310.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 15-17—**Neurolinguistic Programming: Sex and Couples Therapy.** Institute of Sexual Behavior and Institute for Medical Education and Research at Village Inn, La Jolla. Friday-Sunday. 18 hrs. $200. Contact: Inst. of Sexual Behavior, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 15-17—**Substance Abuse Prevention Through Effective Parenting.** Isla Vista Health Projects, Inc., and San Diego State Univ. Student Health Services at Village Inn, La Jolla. Friday-Sunday. $150. Contact: Parenting, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 16—**Review Course for Gynecologic Pathology.** USC at Hilton, Pasadena. Saturday. 6 hrs. $75.

October 16-17—**Thyroid Today—1982, A Clinical Update for the Practicing Physician, First Annual Symposium.** Cypress Foundation at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $130. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

October 16-17—**Medical Psychiatry.** UCSF. Saturday-Sunday. 12½ hrs. $115 before October 1; $135, thereafter. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus, Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 17-19—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn, Napa. Sunday-Tuesday. 12 hrs. $180.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

October 20—**New Concepts in Diabetes.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 21-24—**International Symposium on the Mitral Valve.** Scripps Clinic and Research Fndn. at Hotel del Coronado, Coronado. Thursday-Sunday. 23 hrs. $350. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 22-24—**Practical Gastroentcrology and Flexible Sigmoidoscopy for the Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $275. Contact: Howard D. Groveman, MD, UCSD School of Medicine (M-022), La Jolla 92093. (714) 452-4613.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

October 23—**Current Trends in Cardiovascular Therapy.** Cedars-Sinai Medical Center at Eisenhower Medical Center, Rancho Mirage. Saturday. 8 hrs. $40. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 23-24—**Western Occupational Health Conference—1982.** Western Occupational Medical Assn. at Travelodge at the Wharf, San Francisco. Saturday-Sunday. 10 hrs. $75, members; $95, nonmembers. Contact: WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

October 23-25—**OB and GYN Endocrinology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Monday.

October 23-30—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela. One week. 20 hrs. $275. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 24-25—**Meeting of International Strabismological Association and American Association of Pediatric Ophthalmology and Strabismus.** ISA, AAPOS and PMC at Asilomar, Pacific Grove. Sunday-Monday. Contact: PMC.

October 25-28—**7th Annual Family Practice Update.** LLU. Monday-Thursday. 29 hrs. $225.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

October 27-28—**Vitrectomy.** PMC. Wednesday-Thursday.

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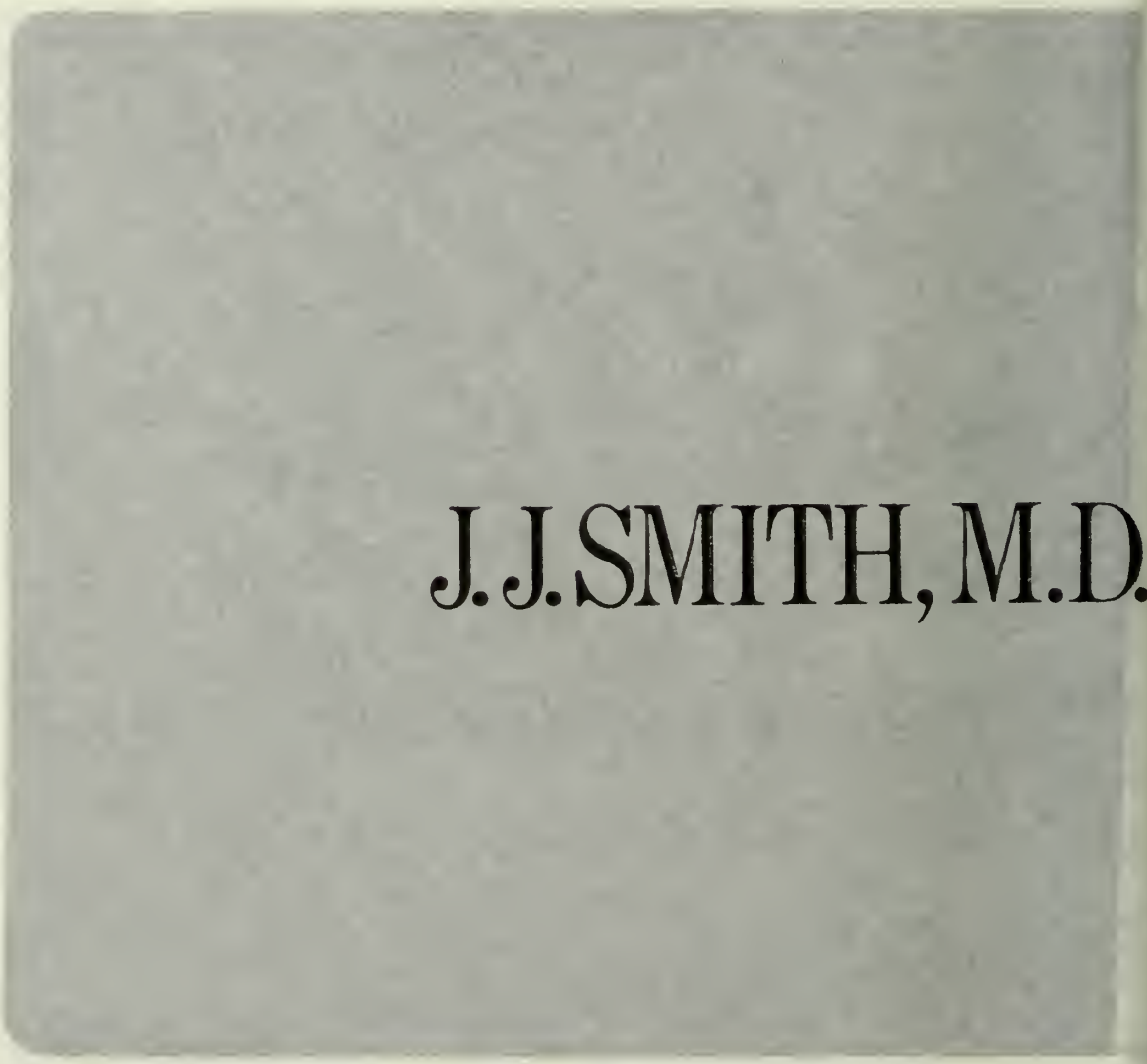

*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counselin can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her moderate to severe sweats and hot flushes. Relieves her discomfort. PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

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IT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to
trophic vaginitis, you're aware of the rapid,
irtually complete relief PREMARIN Vaginal
Cream provides. In the properly selected patient,
not only relieves the distressing symptoms of
estrogen deficiency, such as dyspareunia,
lryness and itching, but it rebuilds vaginal tissue.
PREMARIN Vaginal Cream. You know what it
an do.

onjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal
teoporosis.

ease see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

for atrophic vaginitis

PREMARIN®
(CONJUGATED
ESTROGENS, U.S.P.)
VAGINAL CREAM

0.625 mg/gm

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).
WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.
PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.
ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued, erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism, steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight, reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.
ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.
DOSAGE AND ADMINISTRATION:
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.
Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.
Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.
Osteoporosis (to retard progression)—1.25 mg daily, cyclically.
3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically.* Inoperable progressing prostatic cancer: 1.25 to 2.5 mg three times daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.
Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.
HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. B65—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. B66—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. B67—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. B68—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. B72—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package. Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available—Refill package. Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814/882

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(Continued from Page 16)

October 28-30—**Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 28-30—**2nd Bi-Annual Course in Lower Extremity Trauma: Treatment, Complications and Controversies.** Bone and Joint Disease Foundation at Vacation Village, San Diego. Thursday-Saturday. Contact: Lower Extremity Trauma, P.O. Box 9494, San Diego 92109. (714) 282-9316.

October 29-31—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sahara, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 30—**Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

October 30—**The Troubled Child: Four Practical Approaches.** Del Amo Hospital and American Academy of Pediatrics at Del Amo Hospital, Torrance. Saturday. 4 hrs. $25. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

October 30-November 5—**American Academy of Ophthalmology.** Moscone Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

November 1-3—**Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo Inn, San Diego. Monday-Wednesday. 19 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037.

November 1-4—**Interstate Postgraduate Medical Association—Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., IPMA, P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

November 4-5—**Centennial Sterling Bunnell Memorial Lectureship Program—Surgery of the Hand.** UCSF at Letterman Army Institute of Research, San Francisco. Thursday-Friday. 15 hrs. $250.

November 5—**Comprehensive Care of Genitourinary Trauma.** Orange County Urological Soc. and Western Section, American Urological Assn., at Registry Hotel, Irvine. Friday. 8 hrs. Contact: Kathy DeSantis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

November 5-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 6—**The Sexually Active Adolescent—Implications for the Health Care Professional.** UCLA. Saturday. 7 hrs. $90.

November 6—**Four by George Vaillant: Natural History of Male Alcoholism; Hierarchy of Ego Mechanisms; Work as a Predictor of Mental Health; Case Conference.** Del Amo Hospital, Torrance. Saturday. 7 hrs. $50. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

November 6-7—**Blood Gas and Acid-Base Disorders.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-7—**Invasive Methods and Hemodynamic Monitoring.** STAN. Saturday-Sunday. 15 hrs. $325.

November 6-7—**Trauma.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-8—**Nutrition.** PMC and Institute for the Study of Human Knowledge at San Francisco. Saturday-Monday. Contact: PMC.

November 7-12—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui. Sunday-Friday. $350.

November 7-13—**Allergy and Immune Diseases.** Symposium Maui, Inc., and Hawaii Chap., AAFP, at Lahaina Resort, Kaanapali, Maui. One week. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, HI 96761.

November 10—**Pediatric Emergencies.** LLU. Wednesday. 4 hrs.

November 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

November 10-14—**Sports Medicine Now.** UCD at Hyatt Del Monte, Monterey. Wednesday-Sunday. 24 hrs. $275.

November 11-13—**Critical Decisions in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Thursday-Saturday. 12 hrs. $235. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 11-13—**First National Conference on Infantile Apnea and Home Monitoring of High Risk Infants.** Eisenhower Medical Center and Medical Center of Tarzana at Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: Annenberg Center for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 340-3911, ext. 1661.

November 11-14—**Controversial Areas in Surgery of the Head and Neck.** Institute for Medical Education and Research at Hilton Beach and Tennis Resort, San Diego. 20 hrs. $250. Contact: IMER, P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS Omaha NE 68101. (402) 551-0801.

November 12-14—**28th Annual Group Therapy Symposium.** UCSF at Holiday Inn, Berkeley. Friday-Sunday. 18 hrs. $125. Contact: Aveleen Blumenstock, Asst. Dir., Cont. Ed., Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

November 13—**CT of the Spine.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Saturday. 6 hrs. $95. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049. Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 14—**The Lung in 1982.** Granada Hills Community Hospital and UCLA at Sheraton-Universal, North Hollywood. Sunday. Contact: Germaine Trasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

November 14-17—**California Academy of Family Physicians—Annual Meeting.** Hotel del Coronado Coronado. Sunday-Wednesday. Contact: CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

November 15-19—**An International Perspective on Substance Abuse: The Problem, Its Treatment, and Medical Education.** Assn. for Medical Education and Research in Substance Abuse; World Health Org.; State Univ. of NY Downstate Med. Ctr.; et al at Claremont Hotel, Oakland. Monday-Friday. Contact: Dr. Charles Buchwald, Downstate Med. Ctr., 450 Clarkson Ave.-Box 129, Brooklyn, NY 11203. (212) 270-3150.

November 17—**Controversies in the Management of Early Breast Cancer.** Hospital of the Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

(Continued on Page 32)

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THEO-DUR® (anhydrous theophylline)—**The first and only form of oral theophylline to demonstrate linear blood levels for a full 12 hours in virtually all patients, even those who are rapid metabolizers.**

Until THEO-DUR, blood levels from rapid acting and sustained action theophyllines generally showed unacceptably wide peak-trough fluctuations. This meant the drug was difficult to maintain in the therapeutic range and difficult to sustain in that range for more than a few hours.

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Please see next page for a summary of prescribing information.

THEO-DUR®

(anhydrous theophylline)

Sustained Action Tablets

Today's most widely prescribed bronchodilator.

Description: THEO-DUR Sustained Action Tablets contain anhydrous theophylline, with no color additives

Pharmacologic Actions: The pharmacologic actions of theophylline are as a bronchodilator, pulmonary vasodilator and smooth muscle relaxant since the drug directly relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels. Theophylline also possesses other actions typical of the xanthine derivatives: coronary vasodilator, diuretic, cardiac stimulant, cerebral stimulant and skeletal muscle stimulant. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic AMP which could mediate smooth muscle relaxation.

Indications and Usage: Symptomatic relief and/or prevention of asthma and reversible bronchospasm associated with chronic bronchitis and emphysema

Contraindications: THEO-DUR is contraindicated in individuals who have shown hypersensitivity to any of its components or xanthine derivatives.

Warnings: Excessive theophylline doses may be associated with toxicity; serum theophylline levels should be monitored to assure maximum benefit with minimum risk. Incidence of toxicity increases at serum levels greater than 20 mcg/ml. High blood levels of theophylline resulting from conventional doses are correlated with clinical manifestation of toxicity in: patients with lowered body plasma clearances, patients with liver dysfunction or chronic obstructive lung disease, and patients who are older than 55 years of age, particularly males. There are often no early signs of less serious theophylline toxicity such as nausea and restlessness, which may appear in up to 50% of patients prior to onset of convulsions. Ventricular arrhythmias or seizures may be the first signs of toxicity. Many patients who have higher theophylline serum levels exhibit a tachycardia. Theophylline products may worsen pre-existing arrhythmias.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. This is, unfortunately, true for most anti-asthmatic medications. Therefore, use of theophylline in pregnant women should be balanced against the risk of uncontrolled asthma.

Precautions: THEO-DUR TABLETS SHOULD NOT BE CHEWED OR CRUSHED. Theophyllines should not be administered concurrently with other xanthine medications. It should be used with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, and in the elderly, particularly males, and in neonates. Great caution should be used in giving theophylline to patients in congestive heart failure since these patients show markedly prolonged theophylline blood level curves. Use theophylline cautiously in patients with history of peptic ulcer. Theophylline may occasionally act as a local irritant to G.I. tract, although gastrointestinal symptoms are more commonly central and associated with high serum concentrations above 20 mcg/ml.

Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are:

Gastrointestinal: Nausea, vomiting, epigastric pain, hematemesis, diarrhea

Central Nervous System: Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias

Respiratory: Tachypnea

Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis

Others: Hyperglycemia and inappropriate ADH syndrome.

How Supplied: THEO-DUR 100 mg, 200 mg and 300 mg Sustained Action Tablets are available in bottles of 100, 500, 1000, and 5000, and in unit dose packages of 100.

Caution: FEDERAL LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION

For full prescribing information, see package insert

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J-9043-4 July 1981

A NEW AGE IN THE CONTROL OF ANGINA

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PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:
—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply
—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand
—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page

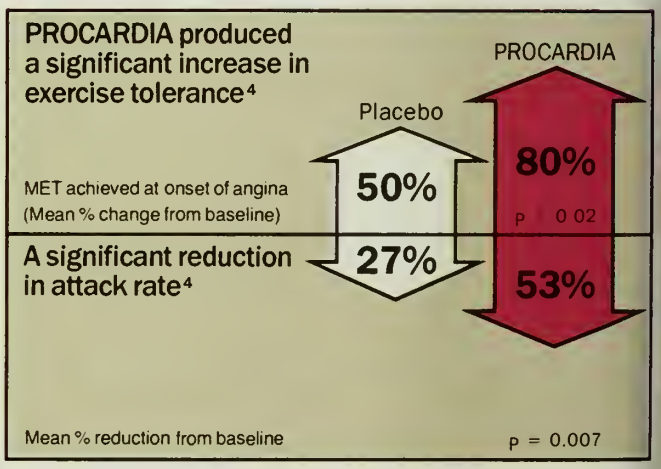
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy)



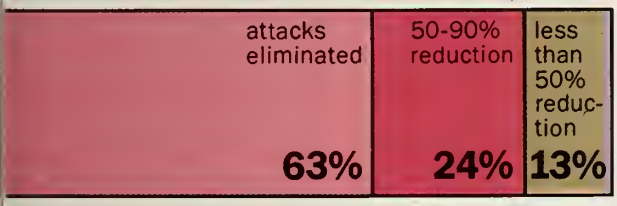
Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

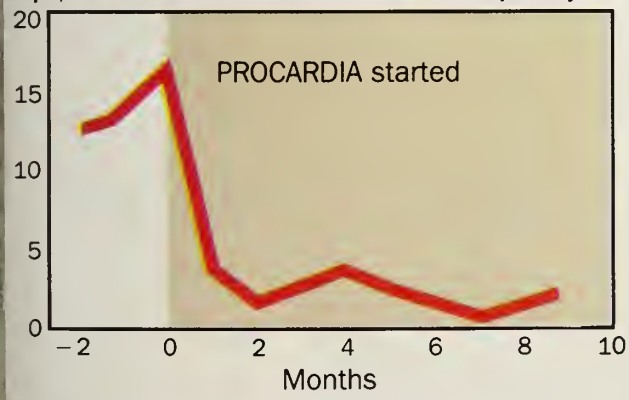
Please see PROCARDIA Brief Summary on last page.

vasospastic angina

OCARDIA eliminated attacks in 63% of patients[5]

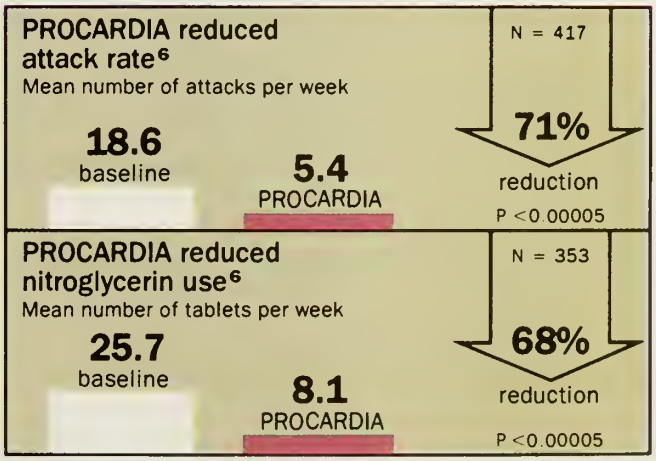


mpt, sustained decrease in attack frequency[5]



g-term, open study of 127 patients unresponsive to beta kers and/or nitrates with symptoms of myocardial emia and demonstrated coronary artery spasm. CARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)



Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

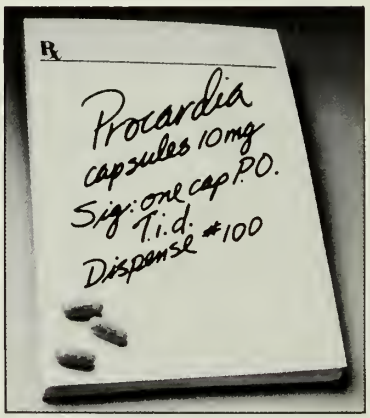
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d.*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

References

1. Lichtlen PR, Engel H-J, Wolf R, et al. Regional myocardial blood flow in patients with coronary artery disease after nifedipine. In Lichtlen PR, Kimura E, Taira N (eds). *International Adalat® Panel Discussion. New Experimental and Clinical Results.* Tokyo, Excerpta Medica, 1978, pp 69–85.
2. Maseri A, Chierchia S. Angina pectoris—a new dimension, a new approach. Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E. *Introduction. New Concepts in Ischemic Heart Disease. The Role of Coronary Artery Spasm.* New York, Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator). Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, April 29, 1982.

PROCARDIA® CAPSULES For Oral Use
(nifedipine)
BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate the peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Pregnancy: Category C.

ADVERSE REACTIONS: The most common adverse events include dizziness, light-headedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in amber glass bottles of 100 capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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(Continued from Page 21)

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 19-21—**Pain Management.** UCLA. Friday-Sunday.

November 19-22—**Pediatric Update.** Calif. Chapters, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 20-27—**3 for 1: Proctology; Psychiatry; Principles.** Univ. of Washington School of Medicine at Sheraton Waikoloa, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

November 21-24—**Pacific Coast College Health Association—Annual Meeting.** PCCHA and San Diego State Univ., Student Health Services, at Hyatt Islandia, San Diego. Sunday-Wednesday. 14 hrs. $40, members; $50, nonmembers. Contact: David Bearman, MD, Student Health Services, San Diego State Univ., San Diego 92182. (714) 265-5281.

November 28-30—**Kids Have Bones, Too.** UCD at Hyatt Del Monte, Monterey. Sunday-Tuesday. 11 hrs.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 3-4—**The Anterior Cruciate Ligament "State of the Art."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 3-4—**Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday-Saturday. 15 hrs.

December 3-5—**Clinical Management of Coronary Disease and Dual-Mode Exercise Testing.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8651.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Fndn. at Hilton Beach Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 4—**Annual Winter Meeting, Emergency Pediatrics, Part II.** Calif. Chapters, American Academy of Pediatrics, at Holiday Inn on Union Square, San Francisco. Saturday. Contact: Beverly Busher, No. Calif. Chap., AAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Ed., Los Angeles 90024. (213) 825-4617.

December 4—**Total Parenteral Nutrition.** UCLA. Saturday.

December 4-5—**MKSAP VI Review Course.** American College of Physicians and UCLA at UCLA. Saturday-Sunday. 12 hrs. $80. Contact: UCLA.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

December 8—**18th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-10—**MKSAP Review Course.** American College of Physicians and UCD at Hyatt Union Square, San Francisco. Thursday-Friday. Contact: UCD.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

December 10-12—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

January 6-9—**Anesthesia Update—1983.** UCSD at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Jordan Katz, MD, Dept. of Anesthesia (M-004), UCSD, La Jolla 92093. (714) 453-7500, ext. 3292.

January 10-14—**7th Annual Hawaii Echocardiography Conference.** Honolulu Medical Group at Westin Wailea Hotel, Maui. Monday-Friday. 30 hrs. $495. Contact: Yvonne Brewer, Honolulu Med. Grp., Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 12—**12th Annual Gastroenterology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375

January 12—**22nd Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday. 4½ hrs. $75. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 12—**Office Urology.** LLU. Wednesday 4 hrs.

January 14-15—**Third Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Bernard L. Tucker, MD, 1136 W. 6th St., Los Angeles 90017. (213) 482-3121.

January 14-15—**10th Annual Santa Clara County Surgical Seminar—Critical Care and Current Concepts.** Santa Clara Co. Surgical Seminar Assn. at Le Baron Hotel, San Jose. Friday-Saturday. 15 hrs. $160. Contact: Surgical Seminar, c/o Kenneth Watanabe, MD, 150 N. Jackson Ave., #209, San Jose 95116.

January 17-18—**International Symposium: The Psychobiology of Alcoholism.** UCLA at Beverly Hills. Monday-Tuesday.

January 17-19—**Society of Thoracic Surgeons.** Hilton, San Francisco. Monday-Wednesday. Contact: STS, 111 E. Wacker Dr., Chicago 60601.

January 17-21—**Interventional Radiology and Diagnostic Imaging Modalities.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $400.

January 20-22—**5th Annual Postgraduate Course on Surgery.** UCD at Holiday Inn, Sacramento. Thursday-Saturday. 15 hrs.

January 22-29—**Advanced Problems in Cardiac Emergencies.** UCSD, American Inst. of Postgraduate Education, Scripps Memorial Hospital at Kona Surf Hotel, Kona, Hawaii. One week. 21 hrs. $325. Contact: AIPE, P.O. Box 2101, Del Mar 92014. (714) 454-3212.

January 22-30—**11th Annual Diagnostic Radiology Seminars.** UCSF at Waiohai Hotel, Kauai, Hawaii. One week. 31 hrs. $350.

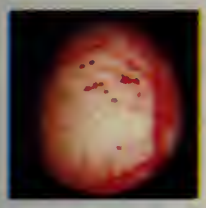
(Continued on Page 34)

WE HAVE A SOLUTION FOR A DIFFICULT UROLOGICAL PROBLEM

The Problem

SYMPTOMS:

EARLY INTERSTITIAL CYSTITIS



CLASSICAL INTERSTITIAL CYSTITIS

- irritative voiding symptoms
- suprapubic pain
- functional bladder capacity reduced
- anatomical bladder capacity:
  - EARLY — normal
  - CLASSICAL — reduced
- vesical mucosa:
  - EARLY — normal appearing
  - CLASSICAL — ulcerated, scarred
- submucosal vesical hemorrhages observed following second overdistension

DIAGNOSIS: INTERSTITIAL CYSTITIS

The Solution

Rimso®-50

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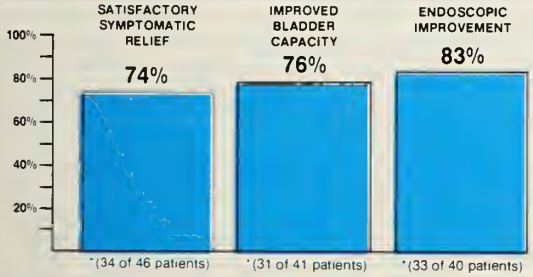
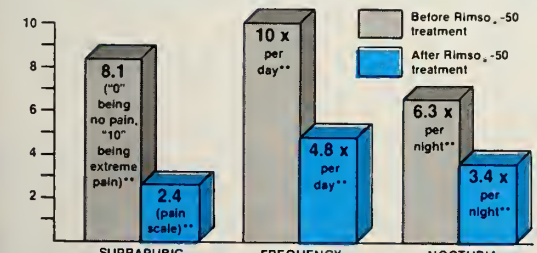
STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE



*STEWART, B.H., et al., J. Urol., 36:116, 1976



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Rimso®-50
(dimethyl sulfoxide)
50% w/w equeous solution

INDICATIONS AND USAGE: Rimso®-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso®-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.
CONTRAINDICATIONS: None known.
WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso®-50. The physician should be cognizant of this possibility in prescribing Rimso®-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.
PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso®-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso®-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide. The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.
DOSAGE AND ADMINISTRATION: Instillation of 50 ml of Rimso®-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of Rimso®-50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested).
HOW SUPPLIED:
Bottles contain 50 ml of sterile and pyrogen-free Rimso®-50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (15° to 30° C).
Do not autoclave.
NDC #0433-0433-05.

*Stewart, B.H., et al., J. Urol., 36:116, 1976

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brand of

STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE

CRYOPRESERVATIVE SOLUTION
(99.0 + concentration)

Available in:

10 ml ampules, 10 ampules/case
70 ml bottles, 6 bottles/case
70 ml multi-dose containers, 6 bottles/case

(Continued from Page 32)

January 24-26—**Midwinter Clinical Conference in Ophthalmology and Otolaryngology.** Research Study Club of Los Angeles at Hilton, Los Angeles. Monday-Wednesday. 21 hrs. $200. Contact: Research Study Club, P.O. Box 49412, Los Angeles 90049.

January 24-28—**Primary Care: Current Management of Common Office Problems.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Tuesday. 33 hrs.

January 26—**Biannual Stroke Symposium.** American Heart Assn., Santa Clara Co. Chap., at Le Baron Hotel, San Jose. Wednesday. Contact: Harriet M. Schutte, RN, PhD, AHA, 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

January 29—**Practical Use of the Visual Physiology Laboratory.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $50. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

January 29—**Ovulation Update: 1983.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. $75. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

January 30-February 4—**9th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 25 hrs.

January 31-February 3—**8th Annual Winter Ski and Study Symposium.** Calif. Chaps. 1 and 2, American Academy of Pediatrics, at Caesar's, Lake Tahoe. Monday-Thursday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 31-February 4—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

ALASKA

November 19-20—**Gastroenterology Conference.** Anchorage. Friday-Saturday. Providence Hospital. For further information, fees, credit and program contact: Mark E. N. Agnew, MA, MB, MRCGP, Director, Medical Staff Education, Providence Hospital, 3200 Providence Drive—Pouch 6604, Anchorage, AK 99502. (907) 276-4511.

IDAHO

See Washington Listings: February 5-12, 12-19, 14-18, 19-26, 26-March 5, 5-12.

MONTANA

September 30-October 2—**Montana Medical Association Annual Meeting.** Great Falls. Thursday-Saturday. Sheraton. For information contact: Montana Medical Association, 2011 Eleventh Avenue, Suite 12, Helena, MT 59601. (406) 443-4000.

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 25—**Margaret E. Prince Lecture on Surgical Aspects of Thyroid and Parathyroid Disease.** Albuquerque. Saturday. Sheraton Old Town. 4 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 6-9—**Annual Microsurgery Workshop.** Albuquerque. Wednesday-Saturday. University of New Mexico Medical Center. 28 credit hours. Contact: Office of CME, UNM School of Medicine, Albuquerque, NM 87131. (505) 277-3942.

October 7-9—**The Clinical Spectrum of Adult Heart Disease.** Albuquerque. Thursday-Saturday. University of New Mexico School of Medicine Auditorium. Hour for hour credit, also AAFP Elective. Contact: Jonathan Abrams, MD, UNM, School of Medicine, Dept. of Cardiology, Albuquerque, NM 87131. (505) 277-4253.

October 8-9—**Diabetes in the Southwest.** Albuquerque. Friday-Saturday. Junior League Building, Old Airport Terminal. 12 credit hours. Also AAFP. Contact: American Diabetes Association, NM Affiliate, 525 San Pedro NE, Albuquerque, NM 87108. (505) 266-5716.

October 9—**Medical and Surgical Management of Cerebrovascular Disease Seminar.** Albuquerque. Saturday. Sheraton Old Town. 7.5 credit hours. Contact: M. J. Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM. (505) 842-7000.

October 14-16—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: NM Heart Institute, 2403 San Mateo NE, Albuquerque, NM 87108. (505) 884-3717.

October 15—**Gynecologic Cancer 1982.** Los Alamos. Friday. Los Alamos Medical Center. 6 credit hours. Contact: James M. Cooper, MD, Los Alamos Council on Cancer, Los Alamos, NM 87544. (505) 662-4412.

November 5-6—**Symposium on Critical Care.** Farmington. Friday-Saturday. San Juan Medical Center. 12 credit hours, also AAFP Prescribed. Contact: San Juan County Medical Society, 814 West Maple Street, Farmington, NM 87401 (505) 325-5011.

November 12-13—**New Mexico Medical Society Interim Meeting.** Las Vegas, New Mexico. Friday-Saturday. Highlands University. 7 credit hours, also AAFP Prescribed. Contact NM Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

February 14-17—**Taos Medical Symposium.** Taos. Monday-

(Continued on Page 53)

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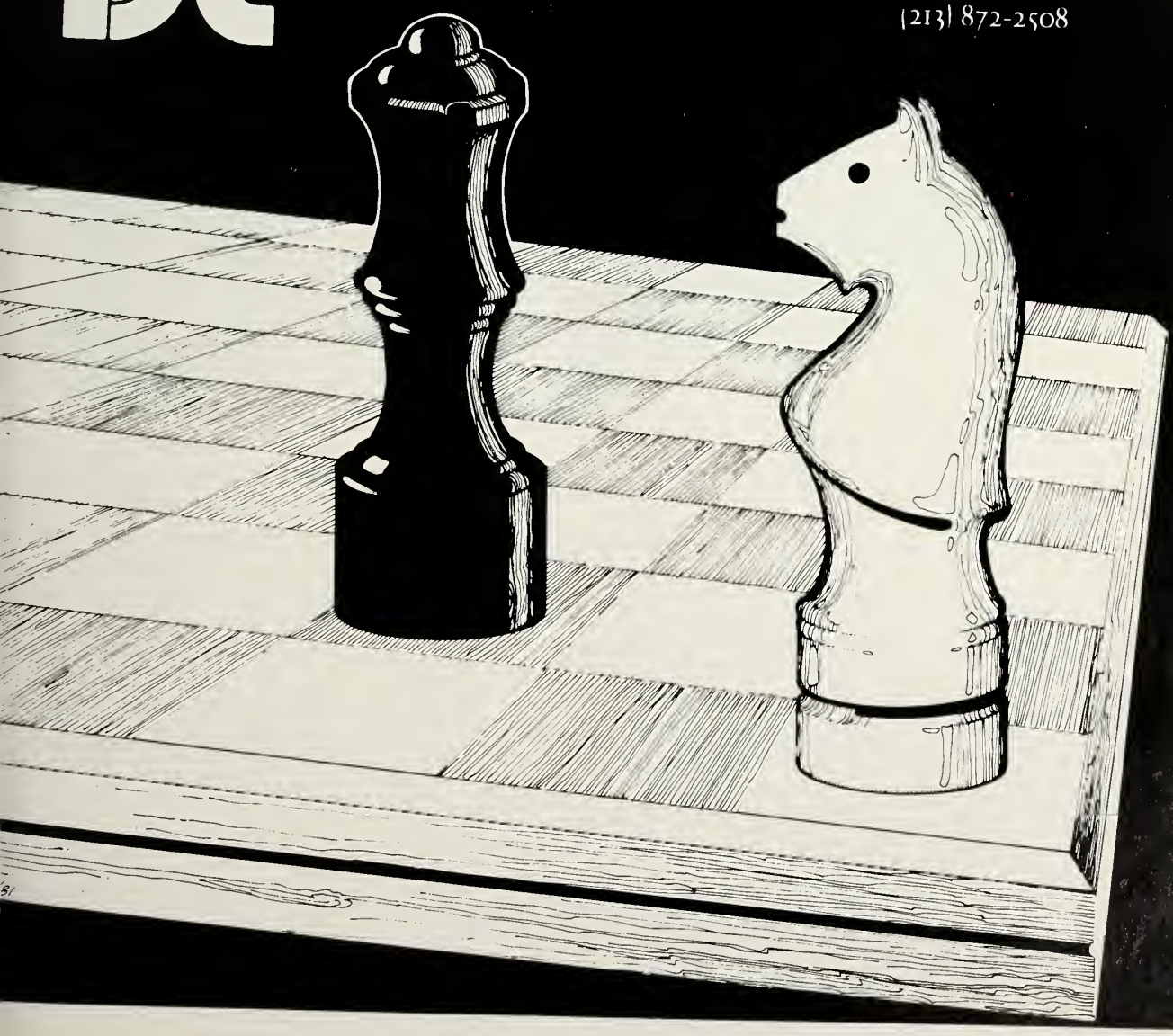

In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

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THE WESTERN
Journal of Medicine

Refer to: Simonowitz DA, Dellinger EP, Oreskovich MR, et al. Anergy in high-risk surgical patients: The role of parenteral nutrition. West J Med 1982 Sep; 137:181-185

Anergy in High-Risk Surgical Patients: The Role of Parenteral Nutrition

DAVID A. SIMONOWITZ, MD; E. PATCHEN DELLINGER, MD;
MICHAEL R. ORESKOVICH, MD; JOSEPH C. STOTHERT, MD, *and*
WILLIAM A. EDWARDS, RPh, *Seattle*

The finding of delayed hypersensitivity on skin testing has been used to predict the outcome following operations, traumas or severe illnesses and has been correlated with nutritional status in some reports. To test these hypotheses, we did weekly skin tests with a battery of four antigens on 98 high-risk patients referred to the nutritional support service. Anergy persisted or developed in 72 patients, whereas 26 patients remained or became reactive. These two groups were comparable in number of days in hospital, age and amount and duration of parenteral nutrition. Infectious complications (68 percent versus 23 percent, P<.001), sepsis (35 percent versus 12 percent, P<.01) and mortality (33 percent versus 0 percent, P<.001) were more prevalent in anergic than in reactive patients. There was no correlation between nitrogen balance studies and skin test results. In most instances conversion of skin test results occurred as a consequence of appropriate surgical care rather than nutritional support. Whereas nutritional support is required in these high-risk patients, anergy should not be the sole indicator for giving nutritional support or delaying an operation.

THE PREDICTIVE VALUE of delayed hypersensitivity shown by skin tests has been established for the outcome of surgical procedures, blunt traumas and nonsurgical illnesses.[1-7] The specific reported association has been between an abnormal skin test response (anergy) and infectious complications, sepsis and mortality. Evidence has also been presented that nutritional support can convert skin test results from anergy to responsiveness and thus improve outcome.[6-10] Others[11,12] have failed to confirm these findings. To examine these correlations, we reviewed the records of patients observed by the Nutritional Support Service (NSS) at Harborview Medical Center (Seattle) over a 12-month period.

From the Departments of Surgery and Pharmacy and the Nutritional Support Service, University of Washington School of Medicine, Harborview Medical Center, Seattle.

Submitted, revised, March 10, 1982.

Reprint requests to: David A. Simonowitz, MD, Dept. of Surgery, RF-25, University of Washington, Seattle, WA 98195.

Methods and Materials

From May 1979 to May 1980 all patients in Harborview Medical Center who required nutritional support by the parenteral route or by tube feeding or jejunostomy were seen by the NSS. Referring physicians agreed to skin testing in 98 of these patients after nutritional support had been begun. The patients were cared for by a resident team under the direction of an attending physician. They were free to follow NSS suggestions or not, and thus not all patients seen by the NSS were skin tested. The NSS assessed the patients'

ABBREVIATIONS USED IN TEXT
NSS=Nutritional Support Service
TPN=total parenteral nutrition

nutritional requirements including calories, protein and trace elements, taking into account the degree of trauma, sepsis and weight loss coupled with age and previous diet. A computer program was used to determine recommended support. All of the cases were followed by the NSS until the patient's discharge from hospital.

Patients were tested initially and at weekly intervals with a battery of four skin tests. An intradermal injection of 0.1 ml of each of the following reagents was given: intermediate-strength purified protein derivative, 5 units (PPD, Ormont Drug and Chemical Company, Englewood, New Jersey); streptokinase, 10 units, and streptodornase, 2.5 units (Varidase, Lederle Laboratories, Pearl River, New York); mumps, 2 units (Eli Lilly and Co., Indianapolis, Indiana), and Dermatophitin, (1:100, Hollister-Steir Laboratories, Spokane, Washington). Reaction was recorded after 48 hours and an induration of greater than 5.0 mm in diameter, excluding erythema, was arbitrarily considered positive.[1] If any one test was positive the patient was labeled reactive; if none were positive the patient was considered anergic. Testing and readings were done by a hospital nurse epidemiologist who was experienced in this technique.

Sepsis was defined in patients with a proved infectious focus (with or without positive blood cultures) progressing to an episode of hemodynamic instability requiring support. Infectious complications without sepsis included wound infections, pneumonia, lung abscess or intraabdominal abscess in patients with hemodynamic stability. For purposes of this report, a patient recorded as being in a septic condition was not recorded a second time as having an infectious complication, so that the overall infection rate is the sum of the rate for sepsis and for infection.

Results

A total of 98 patients were included in this study, 34 women and 64 men, with an average age of 56 years (range, 18 to 98 years). In all, 22 patients had elective operations, 38 were victims of blunt or penetrating trauma requiring surgical treatment and 38 were admitted to hospital with acute problems such as myocardial infarction, perforated or ischemic bowel, pancreatitis or ruptured abdominal aortic aneurysm. The mean duration of stay in hospital for this nutritionally "high risk" group of patients was 39 days (range, 3 to 140 days). A total of 67 patients received total parenteral nutrition (TPN) for a mean of 19 days (range, 3 to 92 days). The remaining 31 patients received enteral nutrition by small-bore feeding tubes. Each patient received an average of 35 kcal per kg of body weight and 1.2 grams per kg of amino acids per day, with appropriate amounts of fats and trace elements.

TABLE 1.—*Reason for Admission to Hospital Correlated With Skin Test Response, Morbidity and Mortality*

	Number	*Number With Sepsis*	*Number With Infections*	*Mortality percent*
Elective				
Anergic	13	1	4	3
Reactive	9	0	0	0
Trauma				
Anergic	29	14	11	7
Reactive	9	2	1	0
Urgent				
Anergic	30	12	7	14
Reactive	8	1	2	0

Of 98 patients seen, 20 (20 percent) were reactive on skin testing when initially seen by the NSS and remained so throughout follow-up. Six more patients were anergic on initial testing but became reactive during follow-up. A total of 26 (27 percent) were therefore reactive or became reactive during NSS follow-up. Of the total, 70 patients (71 percent) were anergic on initial testing and remained so. Two other patients were initially reactive but became anergic during follow-up. Thus, 73 percent were anergic at the end of the NSS follow-up. Because patients were in some instances still recuperating after the initiation of oral feedings, the skin testing sequence occasionally was longer than one-week intervals.

Of the 26 patients in the *reactive group,* nine (35 percent) were admitted following major trauma, eight (31 percent) were admitted for urgent reasons, such as bowel obstruction or perforated viscus, and nine (35 percent) had an elective operation during their stay in hospital. In the *anergic group,* 29 (40 percent) were admitted following major trauma, 30 (42 percent) had an urgent operation and only 13 (18 percent) had an elective operation (see Table 1). The average ages of the two groups were similar: 52 years for the reactive patients and 58 years for the anergic (P =not significant). In addition, the proportion of

TABLE 2.—*Comparison of Patients Who Were Reactive or Anergic to Skin Testing*

	Number	*Mean Age*	*Sex*	*Hospital Days mean*	*Receiving TPN percent*	*Mean Days of TPN*
Reactive patients	26	52	20 ♂ 6 ♀	42	62	23
Anergic patients	72	58	44 ♂ 28 ♀	38	71	17

TPN = total parenteral nutrition

elderly patients in each group was similar (27 percent of the reactive patients was over 70 years old, whereas 32 percent of the anergic patients was over 70 years old). The duration of hospital stay was also similar, with reactive patients staying a mean of 42 days and anergic patients staying 38 days (P = not significant). Most of the patients in each group received parenteral nutrition (reactive, 62 percent; anergic, 71 percent) and the remainder of each group received enteral support either by nasogastric, nasoduodenal or jejunostomy feeding tubes. The duration of this parenteral support was approximately three weeks (reactive, 23 days; anergic, 17 days), indicating a relatively high level of nutritional risk in both groups (Table 2).

There were striking differences in mortality and morbidity between these two groups. In the skin-test reactive group there were no deaths, and there were three patients with sepsis and three with infectious complications, for a combined infectious complication rate of 23 percent. In the anergic group 24 patients died, a mortality of 33 percent. In the anergic group the combined incidence of infectious complications was 49/72 (68 percent), with 27 patients with sepsis and 22 patients with other infectious complications (Table 3). These results are further delineated by reason for admission to hospital in Table 1.

In the anergic group of three patients admitted for elective reasons two died of carcinoma. The remaining 21 patients who died all had unscheduled admissions, and 19 of these died as a result of septic complications. Of 27 patients with sepsis and anergy only seven survived. Thus the mortality in this extremely high-risk group was 74 percent. None of the three reactive patients with an episode of sepsis died ($P < .04$). When the patients are grouped according to the reason for admission (Table 4), there is seen to be a greater incidence of septic complications among the unscheduled patients. Whereas other infectious complications, mortality and anergy were also more common in the unscheduled group, these differences were not statistically significant. There was no significant relationship between skin test reactivity and age (Table 5).

Of the anergic patients, 51 received 35 or more

TABLE 3.—*Comparison of Morbidity, Mortality and Skin Test Results*

Skin Test Results	*Number*	*Number With Sepsis*	*Number With Infections*	*Infectious Complications percent*	*Mortality percent (number)*	*Permanent Coma*
Reactive	26	3	3	23	0	0
Anergic	72	27	22	68	33 (24)	3
P		.01	.05	<.001	<.001	NS

NS = not significant

TABLE 4.—*Morbidity, Mortality and Skin Test Results Versus Indication for Admission to Hospital*

Reason for Admission	*Number*	*Reactive number*	*Reactive percent*	*Anergic number*	*Anergic percent*	*Sepsis number*	*Sepsis percent*	*Infection number*	*Infection percent*	*Mortality number*	*Mortality percent*
Scheduled (elective)	22	9	41	13	59	1	5	4	18	3	14
Unscheduled	76	17	22	59	78	29	38	21	28	21	28
P		NS		NS		.003		NS		NS	

NS = not significant

TABLE 5.—*Skin Test Results and Age*

Skin Test Results	*Age* 0-19	20-29	30-39	40-49	50-59	60-69	70-79	80	*Total*
Reactive	0	5	2	2	5	5	6	1	26
Anergic	1	9	6	5	12	16	12	11	72

kcal per kg of body weight and 1.2 or more grams of protein per kg per day for an average of 17 days. Thirty-one percent were supported for 25 days or more; none of these patients' skin test responses converted to positive, and one patient's test became anergic after having been initially reactive. This patient had multiple intraabdominal abscesses and received parenteral nutritional support for 84 days. Another patient became anergic while receiving adequate enteral nutrition but with a very complicated postoperative course. Only six patients converted to reactivity after having initially been anergic. Five of these six received TPN for an average of 42 days. Two patients converted to reactivity following resection of ischemic bowel. Two patients became reactive after recovering from operations for trauma.

Weekly nitrogen balance (NB) studies using 24-hour urine urea nitrogen determinations[7] were carried out on nine patients while they were receiving parenteral nutrition (NB = nitrogen in − [urine nitrogen determination +4]). Nitrogen losses in fistula or drains were also measured when appropriate and added to the minus side of the equation. Seven of the nine were in positive balance. Five of these seven remained anergic. The remaining two patients converted to skin-test reactivity after attaining positive nitrogen balance in conjunction with appropriate surgical care. The two patients who were in negative nitrogen balance both remained anergic.

Discussion

Palmer and Reed[13] have reported that 91 percent of patients in hospital who are not severely ill will respond to at least one of the four standard skin tests. This was confirmed by Grossman and co-workers,[14] who also noted no significant differences in response with increasing age. Meakins and associates[1] have acquired extensive experience in the use of skin testing to predict outcome of patients in hospital. Their results in 1,332 patients indicated a 36 percent mortality and a 52 percent infectious complication rate in anergic patients, whereas reactive patients had a 4 percent mortality and a 10 percent infectious complication rate. These results were consistent for preoperative, postoperative and trauma cases.[10] In addition, sequential testing showed a 2.1 percent mortality in patients who were initially reactive or whose skin test results showed improvement. In this same group of patients there was a 21 percent infectious complication rate. But those who were initially anergic or who worsened had a 74 percent mortality and a 65 percent infectious complication rate.[15] Pietsch and colleagues[10] showed an association of anergy with sepsis, hemorrhage and age combined with degree of trauma. Anergy was not associated with uncomplicated cancer, nor with age alone.[10] In 50 consecutive elective cases of cholecystectomies reported on by Pietsch and co-workers,[10,16] there were no anergic patients, suggesting that operation alone does not affect skin test results. Others[2-7] have reported a similar predictive value for skin tests. Brown and associates[12] and Ryan and Taft[11] independently found no predictive value for skin testing in solely elective preoperative cases.

Thus, data suggest that response to four standard skin tests can predict outcome following operation or injury and that conversion of anergy to skin test reactivity predicts an improved outcome.[6-10] Whereas several reports[6-10] have attempted to correlate skin test response to nutritional status, Meakins and colleagues[1] have shown that selected anergic patients can convert to reactivity by appropriate surgical care nearly 84 percent of the time.

It was our impression that factors other than nutritional support were important in affecting skin test responsiveness in our patient population. A review of our experience was thus organized to examine this question. It has been previously shown[10,16] that outcome following minor degrees of trauma or surgical procedure was not predicted by skin test results. For this reason we included only those high-risk patients who were judged by their primary clinicians to require intensive nutritional support. There was no statistically significant difference between the reactive and anergic groups in the age, sex, duration of hospital stay, percentage of the groups receiving parenteral nutrition or duration of parenteral nutrition. Thus, these factors did not appear to influence outcome between the two groups. The proportion of elective and nonelective cases in each group was also similar.

Most (73 percent) of the patients in our study were anergic. This is in contrast to other reports in which most patients were reactive.[1-3,5-7] This may be due to the high-risk nature of a group of patients selected solely on the basis of their need for nutritional support.

Our data confirm previous reports that anergic patients have a statistically significant increase in

morbidity and mortality when compared with reactive patients. Anergic patients with sepsis had a 74 percent mortality. Reactive patients rarely became septic (12 percent), whereas anergic patients had a 38 percent incidence of sepsis. While sepsis developed in 31 percent of all of these patients, 90 percent of them were in the anergic group. Thus, there appears to be a strong association between anergy and sepsis in this group of patients. Ryan and Taft[11] and Brown and coworkers,[12] however, did not confirm such a relationship in a group of low-risk patients, all of whom were admitted for an elective operation.

Our data suggest that nutritional support alone will not convert skin test response or improve outcome. Only two of six patients who converted to reactivity appeared to do so primarily because of parenteral nutrition. This was in spite of aggressive nutritional support averaging 42 days in duration with 35 kcal per kg of body weight and 1.2 grams of protein per kg. Most patients who converted to reactivity did so following appropriate medical and surgical care in addition to nutritional support (four of six). Of the anergic patients, 51 received adequate parenteral nutrition for an average of 17 days, with no difference in skin test responsiveness; this included 11 who received 25 days or more and 4 who received more than 40 days of parenteral nutrition. Previous reports[7-9,17] have established that the average time required to convert skin tests in animals and humans is near 18 days. Although our patients received appropriate nutritional support for this length of time, skin test reactivity did not improve in most of the anergic patients. This does not mean that nutritional support was not helpful, but that it was used as a supportive and not a treatment measure.

We were unable to show a correlation of positive nitrogen balance with skin test conversion in a small group of patients. Haffejee and Angorn[18] also failed to show this relationship in patients with esophageal carcinoma.

Thus, based on our experience and that of others, we think that skin test responsiveness does correlate with eventual outcome but that in most cases this outcome is most strongly affected by conventional medical and surgical treatment. Skin testing is a complex procedure that measures a host's ability to put together a number of physiologic processes. It is affected by, but not a direct measure of, nutrition, trauma, sepsis, tumor burden and medication effect. An anergic patient is at high risk for the development of life-threatening complications and must be treated appropriately and expeditiously. Skin test results can be used as one marker for identifying high-risk patients but do not provide a reliable index for designing specific therapy or corrective measures and do not justify altering otherwise standard treatment regimens. Our data are consistent with the hypothesis of Mullen and associates[19] that only in very high-risk patients, as defined by the Prognostic Nutritional Index,[20,21] does parenteral nutrition seem to effect a decrease in incidence of postoperative complications. Parenteral nutrition is required in nutritionally depleted patients as a supportive adjunct regardless of skin test results. In the absence of other indicators of malnutrition, anergy should not be the sole indication for parenteral nutrition or for delay of surgical intervention.

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Hemoglobin E in Indochinese Refugees

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Hemoglobin E, a β-chain variant commonly found in Southeast Asian populations, is relatively unfamiliar to American physicians. The hematologic features of 55 patients with hemoglobin E (8 homozygote, 46 heterozygote and 1 genotype E/β_{thal}) are described and compared with previous series. The patients were immigrants from Cambodia, Laos, Thailand and Vietnam. These studies support the association of this β-globin variant with microcythemia and suggest that it mimics the "thalassemia picture" of microcythemia out of proportion to the degree of anemia. Splenomegaly was not a characteristic. Oxidative hemolysis may occur under conditions that deplete reduced glutathione. The simultaneous presence of the β-thalassemia trait appears to significantly worsen the prognosis.

A VARIETY of hematologic abnormalities are being recognized among Southeast Asians recently arriving in this country. Iron deficiency, minor forms of α- and β-thalassemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency are regularly seen. α-Thalassemia appears particularly prevalent[1,2] and iron deficiency may be due to infestation with the hookworm *Necator americanus*.[3] Another cause of microcythemia, generally unfamiliar to American physicians, is the presence of the hemoglobin (Hb) variant, hemoglobin E (HbE, $\alpha_2\beta_2^{26Glu\rightarrow Lys}$). The HbE gene is carried by an estimated 30 million people, virtually all residing on or near the Southeast Asian mainland.[4-6] Worldwide it is thus one of the most common structural variants.

Awareness of the clinical and laboratory characteristics of this disorder is therefore important to avoid the misdiagnosis of thalassemia syndrome or inappropriate treatment with iron supplements. Furthermore, there is evidence that hemoglobin E may be oxidatively unstable, leading to hemolysis in the presence of certain drugs, serious infections or acidosis. This article describes the experience at one institution with this hemoglobinopathy and reviews some of the literature pertaining to the clinical, laboratory and epidemiologic aspects of this hematologic abnormality.

Patients and Methods

A review of all hemoglobin electrophoresis studies done at St. Mary's Hospital and Medical Center, San Francisco, from January 1977 to October 1981 elicited 55 cases in which hemoglobin E was suspected on initial examination at pH 8.4 on a cellulose acetate medium. It was confirmed in all cases on a citrate agar at pH 6.0. The pathologist's interpretation was reviewed and routine hematologic studies (hemoglobin level, erythrocyte count and cell indices) done by automated methods (Coulter Model S). Target cells on a blood smear had been recorded by technologists.

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ABBREVIATIONS USED IN TEXT

2,3-DPG = 2,3-diphosphoglycerate
G6PD = glucose-6-phosphate dehydrogenase
Hb = hemoglobin
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
MCV = mean corpuscular volume
mRNA = messenger ribonucleic acid

Patient charts were retrospectively reviewed for pertinent historical data and for results of physical examination. No pedigrees were specifically examined.

A total of 46 patients were found to be heterozygous, that is, possessing the HbE trait (genotype AE); eight patients were homozygous (genotype EE), that is, having virtually 100 percent HbE. One 9-month-old female infant was felt to have combined HbE and β-thalassemia traits (E/β_{thal}), and these results are mentioned separately from the above two groups. There were 32 Cambodian patients (29 AE genotypes, 3 EE), 17 Laotian (13 AE, 3 EE and 1 E/β_{thal}), 4 Thai (3 AE, 1 EE) and 2 Vietnamese (1 AE, 1 EE).

Statistical analyses were done using Student's *t* test with a two-tailed distribution. Statistical significance was based on a *P* value less than or equal to .05.

Results

The mean hemoglobin levels, erythrocyte counts and cell indices are presented in Table 1 for the patients heterozygous for HbE. There were no significant racial differences for any of the measurements (Table 2), although the sample sizes of the Thai and Vietnamese patients were too small to allow meaningful statistical analysis.

All but one of the genotype AE cases had microcythemia, with one 34-year-old Cambodian woman having a mean corpuscular volume (MCV) of 82 cu μm (normal, 81 to 99). This patient had rheumatic aortic and mitral valvular disease and acute hepatitis, with evidence of concurrent intravascular hemolysis (corrected reticulocyte count, 4.2 percent, and a low haptoglobin binding capacity of 22 mg per dl). The reticulocytosis may have resulted in slight elevation of her usual MCV into the normal range.

The data from the genotype EE patients are listed in Tables 3 and 4. The lowered hemoglobin level, mean corpuscular volume and mean corpuscular hemoglobin (MCH) are noted, with preservation of the erythrocyte count and mean corpuscular hemoglobin concentration (MCHC).

One of the patients, a 15-month-old Thai male infant (case 1, Table 3), had significantly lower hemoglobin and MCV values than the rest. Electrophoresis showed 91 percent HbE and 9 per-

TABLE 1.—*Hematologic Manifestations of Patients Heterozygous for Hemoglobin E Trait*

	Male Patients (n=21) Mean (range, SD)	*Female Patients (n=25) Mean (range, SD)*	*Male and Female Patients (n=46) Mean (range, SD)*
Age	14 (1–61, 14)	13 (1–62, 17)	14 (1–62, 16)
Hemoglobin level (grams/dl)	12.5 (10.6–15.1, 3.7)	11.5 (8.3–13.8, 3.7)	12.0 (8.3–15.1, 3.7)
Erythrocyte count (million/μl)	5.34 (4.42–6.28, 2.37)	4.99 (3.61–5.96, 2.30)	5.16 (3.61–6.28, 2.34)
MCV (cubic microns)	70.0 (59–77, 10)	69.0 (54–82, 11)	69.0 (54–82, 10)
MCH (picograms)	23.6 (19.5–25.7, 5.1)	23.2 (17.1–27.0, 5.4)	23.4 (17.1–27.0, 5.3)
MCHC (percent)	33.6 (31.1–35.5, 5.9)	33.7 (30.8–36.6, 6.0)	33.6 (30.8–36.6, 5.9)
HbE (percent)	28.0 (17–43, 8)	27.0 (18–37, 7)	28.0 (17–43, 8)

Abbreviations: MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; HbE = hemoglobin E; SD = standard deviation.

TABLE 2.—*Hematologic Manifestations of Patients With Hemoglobin E Trait by Racial Background*

	Cambodian (n=29) Mean (range, SD)	*Laotian (n=13) Mean (range, SD)*	*Thai (n=3) Mean (range, SD)*	*Vietnamese (n=1)*
Age	12 (1–62, 14)	16 (1–61, 16)	1	60
Hemoglobin level (grams/dl)	12.2 (10.3–15.1, 3.7)	11.7 (8.3–13.8, 3.8)	11.2 (9.4–13.2, 3.7)	11.3
Erythrocyte count (million/μl)	5.20 (4.06–6.26, 2.34)	5.10 (3.61–5.87, 2.32)	5.27 (4.57–6.28, 2.41)	4.41
MCV (cubic microns)	70.0 (59–82, 10)	69.0 (54–77, 10)	62.0 (55–68, 10)	77.0
MCH (picograms	23.7 (19.5–27.0, 5.2)	23.0 (17.1–26.1, 5.3)	21.3 (18.8–21.0, 5.1)	25.3
MCHC (percent)	33.8 (31.4–36.6, 5.9)	33.1 (30.8–35.5, 6.0)	34.3 (33.1–35.4, 5.9)	33.5
HbE (percent)	28.0 (18–43, 8)	27.0 (17–35, 7)	26.0 (21–30, 6)	29.0

Abbreviations: MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; HbE = hemoglobin E; SD = standard deviation.

TABLE 3.—*Hematologic Data for Patients Homozygous for Hemoglobin E*

Case	*Age*	*Hb (grams/dl)*	*Erythrocyte Count (million/μl)*	*MCV (cubic microns)*	*MCH (picograms)*	*MCHC (percent)*	*Race/Sex*
1	1	8.9	5.15	49	17.3	36.0	Thai/♂
2	2	11.0	5.78	60	19.1	32.2	Cambodian/♂
3	5	12.2	6.29	58	19.5	33.7	Laotian/♀
4	24	12.4	5.97	64	20.7	32.3	Laotian/♀
5	25	10.7	5.29	61	20.0	32.7	Cambodian/♀
6	26	11.5	5.16	65	22.6	33.7	Vietnamese/♀
7	26	10.3	4.98	62	20.8	33.3	Laotian/♀
8	57	11.0	5.33	60	20.6	34.2	Cambodian/♀

Hb = hemoglobin; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

TABLE 4.—*Hematologic Manifestations of Patients Homozygous for Hemoglobin E Condition (n = 8)*

	Mean (range, SD)
Age	21 (1–57, 18)
Hemoglobin level (grams/dl)	11.0 (8.9–12.4, 3.5)
Erythrocyte count (million/μl)	5.49 (4.98–6.29, 2.38)
MCV (cubic microns)	60.0 (49–65, 9)
MCH (picograms)	20.1 (17.3–22.6, 4.7)
MCHC (percent)	33.5 (32.2–36.0, 5.9)

Abbreviations: MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

cent HbF. Although this was interpreted as indicating a homozygous HbE condition, it is possible that this patient had the E/β_{thal} genotype. Serum iron studies were not done, but no reticulocytosis was noted after 12 days of iron therapy. Another infant, a 9-month-old Laotian female, was not included in this tabulation because her electrophoresis, with 80 percent HbE and 20 percent HbF, was interpreted as E/β_{thal} double heterozygosity. Hematologic data in this case included a hemoglobin level of 9.7 grams per dl, an erythrocyte count of 5.44 million per μl, MCV 55 cu μm and MCH 18.2 and MCHC 32.0 percent. Pedigree studies were not available in either case.

A total of 17 patients were noted to have target cells on blood smear examination: six of eight EE genotype patients (75 percent) and 11 of 46 AE genotype patients (24 percent). Of the six heterozygous patients with hemoglobin levels less than 11.0 grams per dl, five were noted to have target cells.

Splenomegaly was infrequent, being noted in only four patients (three AE, one EE). The spleen became nonpalpable in one of these persons after treatment for malaria. Another heterozygote was G6PD deficient, presenting with active pulmonary tuberculosis and hemolysis.

Two heterozygous patients were treated for *Plasmodium vivax* infections and two had histories of malaria before arrival in the United States.

Discussion

The structural variant, hemoglobin E, was simultaneously described in Thailand and in California 27 years ago.[7-9] At the time of its discovery, the clinical similarity to thalassemia was readily apparent. Persons heterozygous for HbE appeared clinically well, with microcytosis and minimal anemia (mean hemoglobin level 12.6 grams per dl, MCV 82 cu μm),[7] whereas the homozygous state produced the picture of a mild but notable microcytic anemia (mean hemoglobin level 10.5 grams per dl, MCV 69 cu μm),[7] with normal erythrocyte counts and an excess of target cells. Subsequent studies done in that area supported these findings and identified the differing frequencies of this gene in the various populations of the Indian subcontinent.[4,10-12] A relatively high incidence has been seen in Thailand (with gene frequencies in some regions of 30 percent), Cambodia and Burma, with lower frequencies in the Philippines, Vietnam (3 percent) and Malaysia. The disorder is rare among Chinese. The simultaneous presence of β-thalassemia minor and HbE trait (E/β_{thal}) was recognized early as a cause of moderate to severe disability with hemolysis and recurrent transfusion requirements.[7] This disorder is now felt to be the most common symptomatic form of thalassemia in Southeast Asia, surpassing Cooley's anemia.[13,14]

In the aftermath of the Vietnam War, a large number of Southeast Asians have resettled in this country. The results of this study in a group of Indochinese refugees are in agreement with Chernoff and co-workers'[7] original findings in Thailand, with the exception of lower mean corpuscular volumes noted in both the AE and EE geno-

TABLE 5.—*Hemoglobin Values (grams/dl) by Age Group in Patients Heterozygous for Hemoglobin E*

	Males>15 yr.	*Females>15 yr.*	*Males and Females<15 yr.*
Fairbanks et al, 1979[5]	14.3(n= 9)	13.4(n=4)	12.1(n= 8)
This study ..	13.3(n=10)	11.2(n=8)	11.8(n=28)

type persons. A wide range of values was noted in that original work, and the discrepancy may be explained by the differences between the manual technique and the automated method now used. Experience with 21 Southeast Asian refugees, all heterozygous with AE genotype, reported in 1979,[5] showed slightly higher hemoglobin levels in patients over 15 years old (Table 5), though the differences between these results and ours are not statistically significant. Also, unlike our patients, these were asymptomatic family members from kindred studies. The results in our female patients over 15 were weighted downward by two patients with hemoglobins under 9 grams per dl; one was pregnant and another had G6PD deficiency, active tuberculosis and evidence of hemolysis.

Early biochemical studies suggested that hemoglobin E was a variant with low oxygen affinity, the P_{50} (the partial pressure of oxygen at which hemoglobin is 50 percent saturated) being shifted to the right in whole blood of homozygotes and in patients with E/β_{thal} disease.[15] Further studies in heterozygous patients and in diluted solutions of isolated HbE, however, showed normal oxygen affinity.[16] More recently, elevated levels of 2,3-diphosphoglycerate (2,3-DPG) have been found in genotype EE and E/β_{thal} patients, enough to account for the observed shift in the oxyhemoglobin dissociation curve.[17]

Position 26 of the β chain of the hemoglobin molecule is occupied by glutamic acid in all mammalian species so far studied.[18,19] Substitution of lysine at this site produces an electrophoretic mobility distinct from HbA or HbF. Interestingly, a similar substitution of lysine for glutamic acid at positions 6 and 121 results in an identical mobility at pH 8.4 for the variants HbC and HbO_{arab}, respectively. The normal minor hemoglobin, A_2 ($\alpha_2\delta_2$), migrates closely with these variants, and separation of HbE requires the use of an acid buffer. The tertiary conformation of the HbE molecule is important because of the inhibitory effect of the β-26 substitution on the $\alpha_1\beta_1$-interchain contact. This may lead to stereochemical exposure of certain sulfhydryl groups and increased oxidative vulnerability, with precipitation under conditions of oxidative stress.[18] Thus, clinically evident hemolysis may occur in the presence of certain drugs, serious infections or acidosis similar to the hemolysis seen in some patients with G6PD deficiency. Furthermore, this may lead to pronounced variability in hemoglobin levels among affected persons and among levels measured in a given patient at different times.

Physical examination in the absence of hemolysis usually does not disclose any abnormalities. Otherwise unexplained splenomegaly was noted in only 1 of 46 heterozygous patients and 1 of 8 homozygous patients in this study, consistent with previous descriptions.[6,7,12]

The genetic mutation underlying HbE disease leads to reduced β-chain accumulation.[20] α-Globin to β-globin synthesis ratios measured in peripheral blood reticulocytes in homozygous patients are similar to or greater than those normally observed in β-thalassemia heterozygotes, whereas AE genotype patients have consistently higher ratios than normal controls.[14] Low β_E messenger ribonucleic acid (mRNA) levels appear to underlie this phenomenon, and it is possible that the single nucleotide change resulting in the amino acid substitution may also lead to an unstable $\beta/_E$ mRNA structure and degradation at the pretranslational level.[14] Abnormal posttranslational mechanisms do not appear to be involved in reduced β_E-globin production.[21] Phenotypic similarity to β-thalassemia results from this diminished β_E-chain synthesis, analogous to the manner in which the α-chain structural variant, Hb Constant Spring, produces an α-thalassemia-like syndrome.[22] It is thus not surprising that patients doubly heterozygous for HbE and β-thalassemia are substantially more symptomatic than patients heterozygous for either disease.

It remains uncertain why the HbE gene persists in such large numbers in Southeast Asia. Analogous to the sickle cell trait, there may be a survival advantage for the heterozygous condition. Chernoff and associates[7] questioned 560 Thais with HbA for a history of malaria; 270, or 49.7 percent, responded positively. Of 76 persons with HbE (predominantly heterozygotes), 35, or 46 percent, likewise had history of malaria, thus suggesting a lack of protection against the parasite. However, there was no clinical confirmation of the diagnosis in any of the cases, and many febrile illnesses may have been mistaken for

malaria by the native population. Later attempts by Chatterjea[23] to induce infection with *P vivax* suggested resistance in E/β_{thal} heterozygous patients, with 2 of 11 patients acquiring the disease, versus 13 of 14 controls. This resistance was not noted for *Plasmodium falciparum*. Correlation of HbE frequency with the incidence of malaria has been noted in several provinces in Thailand. In 1964 Flatz and colleagues[24] found HbE to be twice as common in the highly malarious hill region as in the plains, where the incidence of malaria is low. In our experience two patients, both of whom were heterozygous, were seen with active *P vivax* infections, and two other heterozygous patients had mentioned a history of malaria.

Conclusion

- The β-chain variant, hemoglobin E, is a common cause of clinical features of a thalassemic condition in Southeast Asian refugees. Distinction from iron deficiency may be made by the normal erythrocyte counts and microcythemia disproportionate to the degree of anemia; the syndrome should be suspected when these findings are noted in an Indochinese patient.
- Because HbE migrates with hemoglobins A_2, C and O_{arab} on routine electrophoresis, additional examination using an acid buffer is required when its presence is suspected.
- Patients who are heterozygous for HbE have normal or minimally reduced hemoglobin levels; homozygous patients may have a mild anemia but generally are clinically well. Splenomegaly is not characteristic of either condition.
- Patients doubly heterozygous for HbE and β-thalassemia are significantly more symptomatic than patients heterozygous for either disorder alone.
- Because HbE is an oxidatively unstable mutation, patients with this disorder, particularly those who are homozygous, must be monitored for hemolysis when experiencing serious infections or when being treated with agents known to deplete reduced glutathione.
- A protective effect against malaria has not yet been established in these patients.

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Refer to: Zacherle BJ, Silver DS: Hot tub folliculitis: A clinical syndrome. West J Med 1982; 137:191-194

Hot Tub Folliculitis: A Clinical Syndrome

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With the increasing use of hot tubs, patients are being seen with a distinct clinical syndrome that appears several hours or days after hot tub exposure. It consists of a maculovesicular, often pruritic rash, and commonly occurring associated symptoms including fever, upper respiratory tract complaints, axillary adenopathy and breast tenderness. Cultures in the cases described here grew out Pseudomonas aeruginosa, *giving a diagnosis of* Pseudomonas *folliculitis. The illness clears spontaneously without any treatment. Proper attention to hot tub chlorination and use are probably important in preventing this problem, and awareness of the syndrome by physicians may prevent unnecessary and costly diagnostic studies and treatment programs.*

THE USE OF home hot tubs and spas is popular in Northern California and is becoming popular elsewhere for relaxation and even social activities. Although this pastime is generally safe, certain health hazards exist. One such problem, *Pseudomonas* folliculitis, has been previously reported in several large groups of people using public hot water soaking facilities in health spas or motels.[1-5] It is now apparent that this can also occur sporadically in persons using home hot tubs. Our report is intended to alert physicians to this entity that may be seen more frequently as home hot tub use becomes more prevalent. We compare our cases with those previously reported to define a distinct clinical syndrome; we also discuss the possible causative factors, the course and complications and the implications of this syndrome for some patient populations.

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Report of a Case

A generally healthy 35-year-old man presented with a pruritic rash and general malaise, which had developed over one day. Physical examination elicited a temperature of 37.9°C (100.2°F). The skin of his trunk, upper arms and thighs had multiple papulovesicular lesions, some of which had pustular apices. The rash did not affect his palms, soles or mucous membranes. Axillary lymph nodes were enlarged, soft and very tender. There was no other adenopathy and the remainder of the examination showed no abnormalities. The pustules were lanced and the material cultured, growing out *Pseudomonas aeruginosa.* Cultures of a blood specimen were negative.

Later the same day, a tender rash developed on the patient's wife and 9-year-old son. Examination confirmed that their skin lesions resembled the patient's, and cultures of specimens from their rash grew the same organism.

Questioning indicated that these three family

members had been in their fiberglass hot tub with two friends about 36 hours before the onset of the patient's rash. A telephone check revealed that the friends had noted a mild rash of similar description, beginning at about the same time as the patient's and clearing spontaneously within two days. In addition, the man and woman both had sore breasts. Cultures were not obtained. An 18-month-old child in the patient's family had been in the hot tub off and on during the day of exposure and each of the following two days. One spot developed on her face that may or may not have been similar to the others' lesions.

A specimen of water from the hot tub was cultured and grew two *P aeruginosa* sp, one of which was identical in growth characteristics to that isolated from the patients' pustules. Serotyping of the *Pseudomonas* organisms was not done.

Affected family members were treated with local application of gentamicin ointment, but because of the axillary adenopathy and fever, the patient also received carbenicillin given orally. The 9-year-old child's symptoms cleared in two days, but the parents' symptoms lasted about seven days. There were no recurrences.

Discussion

Since 1975 five epidemics of documented *P aeruginosa* folliculitis have been reported from whirlpool spas and have involved groups of 27 to 75 people who were clinically ill.[1-5] One report[6] in addition to ours involved cases of two people exposed in their home hot tub. The clinical and bacteriologic aspects of all of these cases are similar. Hot tub folliculitis appears to be a discrete clinical syndrome and may occur in epidemics or as isolated cases.

In all instances there has been an incubation period from exposure to onset of symptoms. In the epidemics reported, the onset occurred from six hours to five days after exposure[1-4] and rashes developed in all five of our patients between 36 and 48 hours after being in the hot tub. The predominant complaint has been rash; lesions are papulovesicular on an erythematous base, 2 to 5 mm in diameter, and some vesicles develop pustular apices. The rash is present on the trunk, buttocks and proximal limbs, usually sparing the face and neck, soles and palms and mucous membranes. It is often but not always pruritic. As with our patients, associated symptoms occur in about half the reported cases and include weakness, myalgia, chills and fever, headache, earache, sore throat, enlarged axillary nodes or tender breasts.[1-5] In three of the previous reports[1,3,6] the rash cleared within ten days—which was similar to our cases. In one series the duration averaged 8 days but varied from 1 to 21 days.[4] Spontaneous healing is the rule though recurrences after initial healing may occur,[4] and Sausker and co-workers[2] described one apparently healthy woman who had several recurrences of follicular pustules over a period of three months following the initial folliculitis.

Few laboratory studies previously reported have included normal complete blood counts; our patient's leukocyte count was 11,900 per cu mm, with 71 percent polymorphonuclear leukocytes. Although Gram stain of material from the pustules was negative, we had no difficulty culturing *P aeruginosa* in specimens from all three of our patients in whom it was attempted. Burkhart and Shapiro[6] also cultured that organism from both of their patients. In larger studies, cultures were less frequently positive for *P aeruginosa* but in those situations many cases were evaluated retrospectively or the patients may have been seen later in their courses. Skin biopsies were done by Sausker and colleagues.[2] They found that the epidermis had minimal acanthosis and spongiosis; the dermis had a heavy inflammatory response with both round cells and polymorphonuclear leukocytes, and there was active folliculitis with disruption of follicular epithelium. Organisms were not identified in the biopsy specimens.

Prevention of hot tub folliculitis ought to be directed at its causes; however, the pathogenesis of this syndrome is not as clear-cut as one might expect, though it certainly is related to *P aeruginosa*.

Disinfection of hot baths would seem paramount and the Centers for Disease Control (CDC) have formulated guidelines for public spas and hot tubs.[7] They specify a free residual chlorine level of at least 1.0 mg per liter (ppm) and suggest regularly hyperchlorinating. One of the previous reports indicated an acceptable chlorine level,[2] though it was determined by the orthotolidine method, which is a less accurate measure of free chlorine than the DPD kit method recommended by the CDC.[7] The hot tub in our report had been chlorinated in the usual manner the day before, but the whirlpool jets had not been turned

on, and the chlorine may not have been well circulated; also, water in the jet system, which grew *Pseudomonas,* may not have been exposed to the chlorine.

The effectiveness of chlorination may depend on additional factors such as organic debris present in the tub from heavy usage and the temperature of the water. Kush and Hoadley[8] have shown that growth of *P aeruginosa* in warm water tubs is enhanced by organic substrate available in the water. Interestingly, in two epidemics[1,4] those exposed persons in whom symptoms developed were clustered in periods of high usage, and in a third epidemic more of the affected people had used the tubs late in the day.[2] Both circumstances might increase the organic substrate available for bacterial growth in the water. All reports of this syndrome are related to high temperature facilities and not to regular swimming pools, though some swimming pools investigated also grew *Pseudomonas.*[1] It has been suggested that high temperatures dissipate chlorination more rapidly than lower temperatures[2] and many *Pseudomonas* sp grow well at 41°C (105.8°F).[9] Japanese standards for tubs require temperatures of at least 42°C (107.6°F), which may suppress bacterial growth.[8] Information is not available in previous reports, but it seems very unlikely that any of the cases referred to in our paper involved pool temperatures that high.

Bathing with soap after soaking may be another deterrent; it reduced the likelihood of rash from 64 percent to 42 percent in Washburn and associates'[1] patients, but it was not significantly protective in that study, two others[2,4] or our own experience.

It has been suggested that *Pseudomonas* is the organism responsible for the folliculitis because of a specific exotoxin or combination of exotoxins that some serotypes might produce.[2] Many *Pseudomonas* exotoxins have been described.[10,11] Furthermore, one serotype, 0:11, has been isolated from patients' lesions and whirlpool water in four of five epidemics.[1-3,5] Against the serotype-specific theory, however, the same serotype was also isolated from whirlpool water at other spas or motels in investigative areas in two reports,[1,2] and at least two other serotypes have been reported in epidemics.[4,5] In other clinical settings, no relationship between site or type of *Pseudomonas* infection and serotype of the infecting organism has been shown.[12]

Not all persons exposed get ill, so host-resistance factors must play a role in whether infection and illness develop. In normal circumstances the invasion of healthy skin by *Pseudomonas* is rare, even though the organism may be present on the skin for a long time.[10] Experimental superhydration of the skin can induce a dense inflammatory *Pseudomonas* folliculitis similar histologically to hot tub folliculitis.[13] Although the experimental conditions are quite different from soaking briefly in a hot spa, it is possible that immersion is important in the breakdown of usual skin resistance in some people.

A predilection for infection might be suspected among persons lacking certain immune responsiveness to *Pseudomonas.* In general, this has been a clinical problem only in diseased patients with leukopenia or other immune deficient states and not in healthy persons.[14]

We are unaware of any report of hot tub folliculitis occurring in a person with diminished immune responsiveness, chronic renal disease or diabetes, or a case of *Pseudomonas* septicemia occurring following hot tub folliculitis. However, we are concerned that such persons might be more susceptible to the disease and perhaps should be warned of the potential risk.

There is no indication that antibiotic treatment, whether systemically or topically administered, is necessary or useful. The illness appears to run its course whether or not antibiotics are used, and it is important for a physician to realize, as we did not, that the presence of associated symptoms does not imply systemic spread of infection.

Conclusion

Hot tub folliculitis may become a more prevalent problem and awareness of the syndrome is important. When a patient presents to a physician without a history of epidemic exposure, especially if that patient frequently uses a home hot tub, but the physician overlooks the possibility that the patient has hot tub folliculitis, other more serious diagnoses will be considered. These include meningococcal or gonococcal septicemia, atypical viral illness, insect bites or scabies, herpes, other bacterial folliculitis, contact dermatitis and iododerma.

The diagnosis of hot tub folliculitis is made by an alert physician by history and physical examination. Usually no laboratory studies are necessary. The treatment is limited to reassurance and

an explanation to the patient of proper hot tub procedures.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Challenge Food Testing for Respiratory Disorders

QUESTION:

Is it accepted medical practice to perform diagnostic evaluation of food allergy as a cause of respiratory disorders?

If yes, is it accepted practice to hospitalize a patient for a 96-hour fast followed by reintroduction of foods into the diet one at a time to observe symptoms? Are other diagnostic methods accepted for evaluation of food allergy as a cause of respiratory disorders?

OPINION:

In the opinion of the Advisory Panels on Allergy, Chest Diseases and Internal Medicine, it is accepted medical practice to perform diagnostic evaluation of food allergy as a possible cause of *certain* respiratory disorders. Although rare, some patients with atopic bronchial asthma and allergic rhinitis are allergic to one or several foods which may, under certain circumstances, exacerbate the respiratory symptoms.

Hospitalization for a 96-hour fast followed by reintroduction of foods to observe symptoms is not an accepted method of diagnosis. There are no scientific data available to support its use; it is unproved and possibly harmful.

Conventional elimination diets and/or double-blind food challenges on an outpatient basis are the accepted medical procedures. Where such methods fail, skin testing by a well-trained specialist and the RAST (radioallergosorbent test) when skin testing cannot be performed are additional accepted diagnostic methods.

Refer to: Marquardt DL, Wasserman SI: Mast cells in allergic diseases and mastocytosis (Medical Progress). West J Med 1982 Sep; 137:195-212

Mast Cells in Allergic Diseases and Mastocytosis

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Mast cells with their stores of vasoactive and chemotactic mediators are central to the pathogenesis of allergic diseases. The cross-linking of receptor-bound IgE molecules on the surface of mast cells initiates a complex chain of events, including calcium ion influx, phospholipid methylation and turnover and cyclic nucleotide metabolism, ultimately resulting in the release of mediators of immediate hypersensitivity. These mast cell mediators are important in smooth muscle reactivity, in the recruitment of eosinophilic and neutrophilic leukocytes and in the generation of secondary chemical mediators. Histologic evidence of mast cell degranulation, biochemical evidence of mast cell mediators in blood and tissues and clinical evidence of signs and symptoms reproducible by these mediators have strongly supported the crucial role of mast cells in asthma, urticaria, anaphylaxis, rhinitis and mastocytosis. Because of their unique location at host environment interfaces, mast cells may both participate in allergic diseases and promote homeostasis.

In 1877 Paul Ehrlich identified granular cells in connective tissue that stained metachromatically with a variety of pure dyes and that he termed mast cells. In the succeeding 105 years, these cells have been studied extensively with regard to their intracellular structure, granular contents, mode of activation and biochemistry of secretion. The release of granular constituents, the chemical mediators of immediate hypersensitivity, and their subsequent action on surrounding cells and tissues are thought to be major factors in the pathophysiology of asthma, urticaria, rhinitis, anaphylaxis and systemic mastocytosis, and at least a minor component of several other disorders. In this review, "normal" mast cell structure, biochemistry and function will be discussed, and consideration will be given to the contribution of the mast cell to several disease states.

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Physiology and Biochemistry of Mast Cells

Appearance and Location

Mast cells are generally located near small blood vessels, nerves and lymphatics at a concentration in human lung tissue and skin of 1 to 10 million cells per gram.[1] They are found in abundant amounts in loose connective tissue, skin, lymphoid tissue and respiratory epithelium and are found free in bronchial lumina, in bone marrow and in the submucosal layers of the digestive tract.[2-5] Their location at the host-environment interface

ABBREVIATIONS USED IN TEXT

Ca^{++} = calcium
cAMP = cyclic 3′,5′-adenosine monophosphate
Con A = concanavalin A
ECF-A = eosinophil chemotactic factor of anaphylaxis
ETYA = eicosa-5,8,11,14-tetraynoic acid
HETE = hydroxyeicosatetraenoic acid
HHT = 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid
HMW-NCF = high molecular weight neutrophil chemotactic factor
5-HPETE = 5-hydroperoxyeicosatetraenoic acid
PAF = platelet-activating factor
SRS-A = slow-reacting substance of anaphylaxis

allows mast cells to readily participate in allergic and inflammatory reactions. Mast cells are found free in the rat peritoneal cavity, and this ease of access has made rats a common source for obtaining mast cells for experimental purposes.

Mast cells measure 10 to 15 μm in diameter and have an ovoid shape and a ruffled-appearing plasma membrane. They are most notable for the presence of numerous dense metachromatic-staining secretory granules 0.2 to 0.5 μm in diameter, which in humans have a scroll or whorllike appearance. They also possess several types of cellular organelles, including a nucleus, nucleoli, ribosomes, endoplasmic reticulum, mitochondria, Golgi's apparatus and microfilaments. The cells may be stained by single, pure, metachromatic dyes such as toluidine blue, azure A, methyl green or methylene blue.[2,5]

The origin of mast cells is still subject to some speculation, but the likely precursors include primitive mesenchymal cells, fibroblasts, lymphocytes, thymocytes or bone marrow-derived cells. The perivascular, perilymphatic location of mast cells in connective tissue and their relatively fixed position support the theory of an undifferentiated mesenchymal precursor that differentiates locally.[6] That mast cells appear in cultures of tissue specimens of rodent thymus gland suggests that thymocytes or lymphocytes may provide factors helpful in the production of mast cells.[7] The prominence of mast cells in bone marrow in similar numbers to lymphocytes raises the possibility of a bone marrow precursor of mast cells.[8] Furthermore, a select mouse genotype, W/W^V, characterized by anemia and mast cell deficiency, shows a prominent increase in tissue mast cells after bone marrow transplantation.[9] Taken together, these findings do not provide a definitive source for mast cells and imply that they may have more than one type of precursor, depending on their location and the species under consideration.

Mast cells and basophils are similar in that they both possess IgE receptors on their cell surface membranes and both contain histamine. However, basophils are a part of the polymorphonuclear leukocyte series and originate in bone marrow,

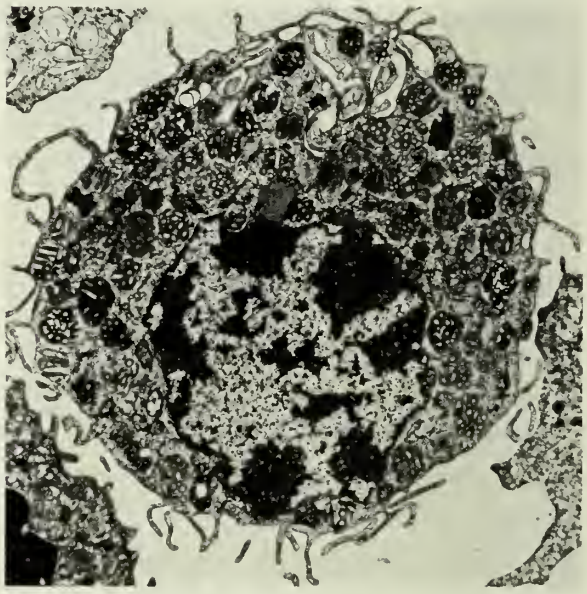

Figure 1.—Human lung mast cell. The cell membrane is reduplicated, the nucleus round and the granules have an intricate subgranular structure. Reproduced with permission from the Journal of Cell Biology (1980; 85:299-312).

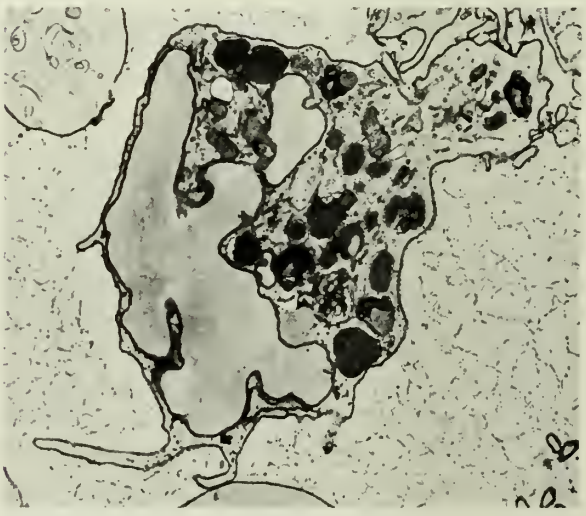

Figure 2.—Human peripheral blood basophil. The cell membrane is relatively smooth with a multilobed nucleus; the cytoplasmic granules possess no structural organization. Reproduced with permission from Laboratory Investigation (1980; 43:126), copyright 1980, U.S./Canadian Division of the International Academy of Pathology.

have no structural organization to their granules, may degranulate one granule at a time and do not contain heparin (Figures 1 and 2).[10] Basophils circulate in the bloodstream and are prominent in tissue in delayed-type hypersensitivity reactions, most notably contact dermatitis.

Granular Contents

The secretory granules of mast cells have been examined most extensively in rat peritoneal mast cells, but some comparative studies of purified human lung mast cells have recently become available. About two thirds of the granule mass is made up of protein, only a portion of which has been specifically characterized. The mast cells possess proteases, notably chymase in rats[11] and a tryptase in humans,[12] and B hexosaminidase,[13] β-glucuronidase[13] and arylsulfatase,[14] suggesting the secretory granules represent modified lysosomes. About a third of the mast cell granule content is macromolecular heparin proteoglycan with a molecular weight of approximately 750,000.[15] The heparin molecule is highly negatively charged, and this property is thought to play an important role in the structural integrity of the granule. Both rat peritoneal and human lung mast cell granules contain the preformed mediator, histamine, bound ionically to the granular matrix, at concentrations of about 25 μg per million cells and 5 μg per million cells, respectively.[16] Rat and mouse mast cells also contain serotonin at concentrations of nearly 2 μg per million cells,[17] and dopamine has been found in small quantities in mast cell granules from some mammals.[4]

Secretagogues and Secretion

Numerous naturally occurring and exogenous agents are able to stimulate mast cells to degranulate and release their stored chemical mediators (Table 1). Perhaps the most pathophysiologically important are the IgE-dependent mechanisms, which account for immediate hypersensitivity reactions. IgE is an immunoglobulin with a molecular weight of approximately 190,000, composed of two light chains and two heavy chains linked covalently by disulfide bonds. The light chains are either k or λ as in other immunoglobulin classes, but the heavy chains are unique in that they contain five complete domains with disulfide bonds between them, and their Fc regions bind avidly to specific receptors on mast cells and basophils.[18] The IgE receptor is comprised of an α-subunit with a molecular weight of 50,000, a part of which binds IgE, and a β-subunit with a molecular weight of 30,000.[19] Rat mast cells have 300,000 such receptors per cell,[20] and when the receptor-bound IgE molecules are cross-linked, mast cell mediator release is initiated.[19] This cross-linking may occur with multivalent antigens, intact antibody to IgE or divalent Fab_2 fragments of anti-IgE, or antibodies to the IgE receptor itself, suggesting that a physical bridging of adjacent receptors is needed to produce mast cell activation and mediator release.[21] In humans the level of circulating IgE in serum correlates well with the number of IgE molecules per basophil and presumably per mast cell.[22] Generally, about 10 percent of IgE receptor sites are occupied, but atopic persons with high serum IgE levels may have up to a 95 percent receptor occupancy rate and, interestingly, often have a larger number of IgE receptors per basophil than normal persons.[22] Whether high levels of IgE cause upregulation of IgE receptor number by a positive feedback mechanism or whether the IgE receptor number is established at birth and correlates with high IgE levels is not known.

Mast cells may also be degranulated by several non-IgE-dependent agents including the anaphylatoxins, C_{3a} and C_{5a}, concanavalin A (Con A), compound 48/80 and other polyamines, the cal-

TABLE 1.—*Mast Cell Secretagogues That Function In Vivo*

- Immunologic mechanisms
  - IgE-mediated
  - IgG reagins (?)
  - Immune complexes
    - Complement activation (C3a, C5a generation)
    - Direct activation by receptor cross-linking
- Nonimmunologic mechanisms
  - Direct mast cell degranulation
    - Drugs
      - Narcotics
      - Curare
      - Succinylcholine
      - Polymixin B
    - Radiocontrast media
    - Complex carbohydrates
    - Venoms
    - Irradiation
  - Arachidonic acid metabolism alteration
    - Aspirin
    - Nonsteroidal antiinflammatory agents
    - Tartrazine (? lipoxygenase pathway)
  - Complement activation (C3a, C5a generation)
    - Blood products
    - Radiocontrast media
    - Via cleavage by active enzymes

cium ionophore A23187, complex carbohydrates such as dextran, adenosine triphosphate, endotoxins, bee and snake venom proteins and drugs such as narcotics, *d*-tubocurarine, succinylcholine chloride and polymyxin B sulfate.[2,5] These secretagogues act through several different mechanisms, but in general are energy and calcium (Ca^{++}) dependent, result in the uncovering of a serine esterase and cause alterations in membrane lipids.[23]

When a secretagogue acts on the mast cell plasma membrane, usually at specific membrane receptors, subcellular events result in the opening of membrane calcium channels with a brisk calcium influx associated with granule swelling and fusion of granule membranes to each other and to the plasma membrane (Figure 3).[24] This fusion exposes the granular contents to the extracellular environment, where ion exchange with sodium causes the release of mediators that are bound to the granule by low affinity charge interactions such as histamine and eosinophil chemotactic factor.[25] Finally, the mast cell granule may actually be extruded from the cell. The macrophages, neutrophils and eosinophils that accumulate in response to the chemotactic mast cell mediators phagocytose the granules within 24 hours and appear to degrade the granule matrix.[6,26]

Biochemistry of Secretion

A variety of biochemical events take place before mast cell secretion, including changes in cyclic 3′,5′-adenosine monophosphate (CAMP) levels,[27] ionized calcium fluxes,[28] phospholipid methylation,[29] membrane phospholipid turnover,[30] arachidonic acid metabolism,[31] intracellular protein phosphorylation,[32] and the uncovering of a serine esterase (Figure 4).[33] The process requires a source of energy, usually glycolysis, because 2-deoxyglucose in the absence of glucose may suppress mediator release.[34] Although the need for these events is well established, the ordering, relative importance and interrelationship of these pathways remains to be discerned.

cAMP. That CAMP levels fluctuate before and during stimulated mediator release from rat serosal mast cells and mammalian lung fragments is well documented,[27,35] but the precise significance of these changes remains an enigma. The early findings that β-adrenergic agonists and theophylline, both known to increase cellular levels of CAMP, acted synergistically to inhibit IgE-mediated release of histamine and slow-reacting substance of anaphylaxis (SRS-A) from lung fragments, and that β-adrenergic antagonists or α-adrenergic agonists, which decrease CAMP levels, enhanced mediator release, suggested a role of CAMP in the regulation of mast cell secretory events.[36,37] A generalization that became popular was that agents acting to increase CAMP levels inhibit mediator release whereas those that decrease

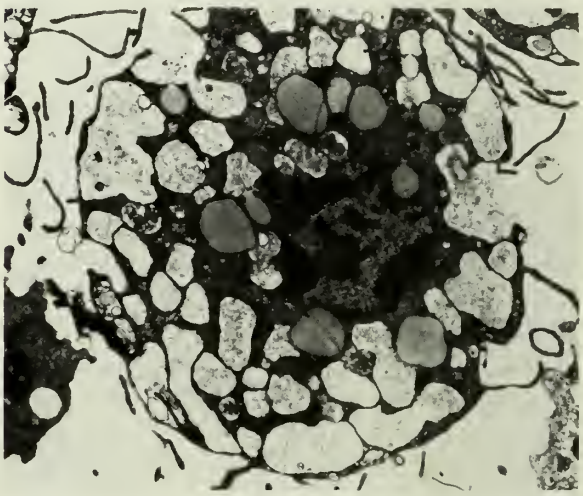

Figure 3.—Human lung mast cell after IgE-dependent activation. Note the granule swelling, loss of subgranular structure, granule fusion and partial granule solubilization. Reproduced with permission from the Journal of Cell Biology (1980; 85:299-312).

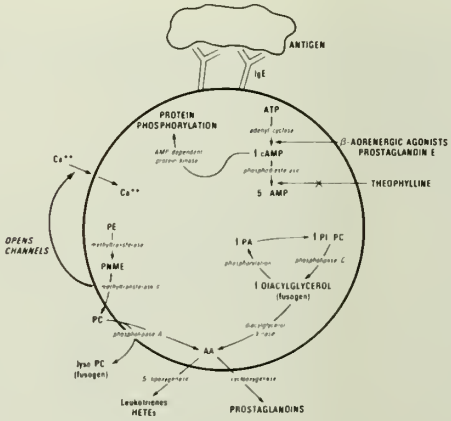

Figure 4.—Simplified schematic diagram of phospholipid methylation, cyclic nucleotide metabolism and phospholipid turnover in a mast cell. Although these cellular events are important in the biochemistry of mast cell activation, their interrelationships have not been defined. Abbreviations: AA = arachidonic acid; ATP = adenosine triphosphate; Ca^{++} = calcium; cAMP = cyclic 3′,5′-adenosine monophosphate; HETE = hydroxyeicosatetraenoic acid; PA = phosphatidic acid; PC = phosphatidylcholine; PE = phosphatidylethanolamine; PI = phosphatidylinositol; PNME = phosphatidyl-*N*-monomethylethanolamine.

cAMP levels augment release. The data, however, were obtained mostly from mixed cell systems.

Studies of purified rat peritoneal mast cells permit analysis of cAMP changes in a single cell type and show varied changes in cAMP levels, depending on the stimulus for activation.[27,38] In most release systems, including those using IgE cell surface receptors, there is a monophasic rise in cAMP levels 5 to 15 seconds after activation that precedes the release of histamine from the mast cells.[27,39] Several investigators have also identified a second monophasic rise in cAMP that occurs after histamine release has peaked, can be suppressed by inhibitors of the cyclooxygenase pathway of arachidonic acid metabolism and is thought to be due to the endogenous mast cell formation of prostaglandin D_2.[39] Contrary to the "increase in cAMP/decrease in mediator release" noted in lung tissue is the finding that prostaglandin D_2 produces a twofold to threefold rise in cAMP but does not inhibit immunologic mediator release from purified rat serosal mast cells.[40] Adenosine[41] and purine-ring modified adenosine analogs also potentiate the early rise in mast cell cAMP associated with activation yet enhance mediator release, whereas ribose-modified adenosine analogs suppress mediator release and decrease adenylate cyclase activity.[42] The crucial factor in cAMP enhancement of mast cell mediator release is the subsequent activation of a cAMP-dependent protein kinase.[43] In IgE-mediated secretion, the initial monophasic cAMP rise is associated with activation of cAMP-dependent protein kinases, whereas cAMP increases caused by prostaglandin D_2 do not affect this intracellular intermediary.[44] In addition to, or as a consequence of, their role in cAMP-dependent protein kinase activation, cyclic nucleotides may also affect secretory granule release by their influence on mast cell microtubule polymerization.[45]

Ionic calcium. Calcium, in a mechanism called stimulus-secretion coupling, is required for several types of secretory cells to extrude their granules.[46] The mast cell intracellular calcium concentration is more than 10,000 times less than the extracellular calcium concentration, and this disparity is maintained by channels for energy-dependent calcium efflux, transport of calcium coupled to sodium transport by an electrochemical gradient and binding of calcium to cytoplasmic structures including glycoproteins and organelles.[47] The importance of calcium in the mast cell mediator-release reaction has been verified in that most secretagogues, with the exception of compound 48/80, which seems to mobilize intracellular calcium stores, require some extracellular calcium to accomplish the secretory process.[2] Calcium uptake occurs immediately before histamine release in rat mast cells stimulated by anti-IgE or the calcium ionophore.[48] The latter is thought to activate mast cells by interacting with cell membrane lipids, forming hydrophobic calcium complexes and thereby facilitating calcium transport down its concentration gradient.[49]

Phospholipid methylation. Some studies show that within 15 seconds after rat mast cells are stimulated with antibodies against IgE receptors and bridging of the IgE receptors occurs, a transient marked increase in ^{3}H-methyl incorporation into membrane lipids takes place, which returns to baseline in 30 seconds.[48] Even in studies that fail to show IgE enhancement of phospholipid methylation, the activation of mast cells by IgE-dependent stimuli in the presence of inhibitors of the methyltransferase reactions is associated with a fall in ongoing methylation, inhibition of the expected calcium influx and inhibition of histamine release.[50] Taken together, these findings suggest that membrane phospholipid methylation is a prerequisite for mast cell mediator release stimulated by anti-IgE. However, degranulating agents that do not cross-link IgE molecules, such as 48/80 and A23187, do not stimulate phospholipid methylation.[29] Biochemical studies of many types of cells including mast cells that methylate phospholipids have shown the presence of two methyltransferase enzymes, the first facing the cytoplasmic side of the membrane and methylating phosphatidylethanolamine to phosphatidyl-*N*-monomethylethanolamine, and the second facing the outer surface of the membrane methylating phosphatidyl-*N*-monomethylethanolamine to phosphatidylcholine.[51] During the presumed translocation of phospholipids from the cytoplasmic side to the outside of membranes by successive methylation, membrane viscosity is likely to be reduced, conceivably opening channels for calcium ion influx. Phospholipase A_2, which catalyzes the hydrolysis of phosphatidylcholine to arachidonic acid and lysophosphatidylcholine, requires calcium for its actions and this calcium influx may help activate the enzyme.[52] Arachidonic acid release from rat leukemic basophils is preceded by phospholipid methylation and augmented by antigenic stimulation,[53] whereas lysophosphatidylcho-

line is a detergentlike fusogen that stimulates mast cell secretion.[54]

Phospholipid turnover. Resting mast cells have been shown to preferentially incorporate $^{32}PO_4$ into membrane phosphatidic acid, phosphatidylinositol and phosphatidylcholine. When mast cells are stimulated with anti-IgE, compound 48/80, Con A or the calcium ionophore A23187, markedly increased labeling of phosphatidic acid occurs within 8 seconds, followed within 30 seconds by labeling of the other two phospholipids.[50] These changes occur before and during the release of mast cell mediators and may be provoked by similar concentrations of the secretagogues required to provoke mediator release. Agents such as theophylline that modulate CAMP metabolism and inhibit histamine release similarly inhibit mast cell phospholipid labeling,[55] and agents that modulate the lipoxygenase pathway of arachidonic acid metabolism such as eicosa-5,8,11,14-tetraynoic acid (ETYA) inhibit both stimulated mast cell mediator release and phospholipid turnover.[56] The parallel changes in phospholipid metabolism and mediator release suggest that mast cell phospholipid metabolism is a central event in the biochemistry of the mast cell secretory process, possibly at least partially through the action of phospholipase C, which produces diacylglycerol from a precursor phospholipid molecule. Levels of diacylglycerol, a potent agent inducing membrane fusion, rise twofold to fourfold during mast cell activation.[57] Phosphorylation of diacylglycerol generates phosphatidic acid, and as this latter molecule is noted to increase within eight seconds of mast cell activation, it is possible that activation of phospholipase C is the earliest step in mast cell mediator release.

Arachidonic acid. Recent studies indicate that arachidonic acid metabolism is required for mast cell mediator release.[31] Arachidonic acid would be made available to the mast cell by either the action of phospholipase A_2 on intact phospholipids or by the sequential action of phospholipase C and diacylglycerol lipase. Arachidonic acid is then metabolized through two major pathways, a 5-lipoxygenase pathway that generates 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and thence the leukotrienes and hydroxyeicosatetraenoic (HETE) acids and a cyclooxygenase pathway resulting in the formation of prostaglandins and thromboxanes.[58] The cyclooxygenase inhibitors, aspirin and indomethacin, in concentrations up to 60 μmol per liter, have no effect on mediator release, suggesting that mast cell cyclooxygenase activity is not necessary for the release process to take place. However, ETYA, an inhibitor of both the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism does inhibit histamine release induced by anti-IgE, Con A or A23187, indicating that patency of the lipoxygenase pathway may be crucial for mast cell secretion.[31] Moreover, 5-HETE and 12-HETE, lipoxygenase products, enhance IgE-mediated secretion.[59]

Resting and activated mast cells seem to metabolize arachidonate somewhat differently. When resting cells are preincubated with free arachidonic acid and subsequently stimulated, mediator release is partially inhibited.[31] This inhibition is blocked by aspirin or indomethacin, implying that resting cells generate a cyclooxygenase product during arachidonic acid metabolism that may render mast cells partially refractory to secretory signals. However, once mast cell secretion is under way, the addition of exogenous arachidonic acid actually enhances mediator release, perhaps due to the generation of lipoxygenase products.[31]

Intracellular protein phosphorylation. Rat mast cells stimulated with 48/80 or A23187 within ten seconds phosphorylate three mast cell proteins with molecular weights of 68,000, 59,000 and 42,000 in a calcium-dependent process. A fourth protein of molecular weight 78,000 is phosphorylated 30 to 60 seconds after 48/80 (but not A23187) stimulation when secretion is well under way.[32] When mast cells were prelabeled with ^{32}P and incubated with sodium cromoglycate, a drug that inhibits mast cell mediator release by unknown mechanisms, only the phosphorylation of the 78,000 molecular weight protein was enhanced, again relatively late in the course of the response.[60] From these results it has been postulated that the early protein phosphorylation seen after mast cell activation may be related to the exocytotic secretory response, whereas the late phosphorylation of the 78,000 molecular weight protein might be a component of the mechanism of calcium-gate closure. Other investigators recently identified an early phosphorylation of the IgE receptor of rat mast cells within 15 seconds after stimulation by A23187 and suggest the possibility that this step may be important in transmitting extracellular signals into the cell.[61] These phosphorylation steps presumably are dependent on adenylate cyclase generation of CAMP and

activation of the CAMP-dependent protein kinases (see above).

Serine esterase. The need for uncovering of a serine esterase for mast cell secretion to occur is suggested by the fact that isoflurophate, an irreversible serine esterase inhibitor, prevents antigen-induced mediator release from rat serosal mast cells and human lung fragments.[33,62] If isoflurophate is added to unstimulated cells but removed before activation, no effect on mediator release is seen, suggesting that the esterase is protected in resting cells. There is no direct evidence other than these studies that these organophosphorus inhibitors are acting only on the serine esterase and do not interact with mast cells in some other way to inhibit the secretory process.

Although it is not possible at the present time to be certain of order and interrelationship of these various biochemical processes in mast cell activation, it is tempting to speculate that the initial bridging of IgE molecules activates two basic but related processes, namely phospholipid metabolism and CAMP generation. The metabolism of phospholipids would be expected to generate fusogenic substances which enables membrane fusion, to liberate arachidonic acid, which enables enhanced mediator release via 5-HETE and 12-HETE, and to alter membrane fluidity, which permits adenylate-cyclase coupling to protein kinase and perhaps enhances Ca^{++} ion flux. Concurrently, adenylate-cyclase activation and generation of CAMP would be translated by CAMP-

TABLE 2.—*Vasoactive Smooth Muscle Reactive Mediators*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Histamine (mast cell basophil)	Preformed	H_1: Contract smooth muscle Increase vascular permeability Increase cGMP Generate prostaglandins	Classical antihistamine
		H_2: Increase vascular permeability Increase gastric acid secretion Increase cAMP Stimulate suppressor T lymphocytes	Cimetidine
Serotonin (platelet)	Preformed	Increase vascular permeability Contract smooth muscle Released by PAF action	Hydroxyzine Cyproheptadine
Arachidonic acid metabolites			
Leukotrienes C_4,D_4,E_4 (SRS-A) (neutrophils macrophages mast cells ?)	Generated	Constrict smooth muscle Increase vascular permeability Decrease peripheral blood flow (C_4) Vasodepressors Synergistic with histamine Generate prostaglandins	Glucocorticoids may prevent generation
Prostaglandins	Generated		Aspirin and nonsteroidal antiinflammatory agents block generation
D_2 (mast cells)		Increase cAMP level Contract smooth muscle Increase vascular permeability	
E_2 (many cell types)		Relax smooth muscle	
$F_2\alpha$ (many cell types)		Increase cAMP level, contract smooth muscle	
I_2 (prostacyclin) (many cell types)		Decrease cAMP level Contract smooth muscle	
Thromboxane A_2 (many cell types)		Increase cAMP level Inhibit platelet aggregation Contract smooth muscle Induce platelet aggregation	
Platelet-activating factor (mast cells ? macrophages neutrophils)	Generated	Aggregate platelets Release platelet amines Sequester platelets in tissue Induce vascular permeability Vasodepressor Vasoconstriction Bronchoconstriction	None

cGMP = cyclic guanosine monophosphate; cAMP = cyclic 3′,5′-adenosine monophosphate; PAF = platelet-activating factor; SRS-A = slow-reacting substance of anaphylaxis.

dependent protein kinase activation into the phosphorylation of key proteins, some of which may regulate calcium influx, intracellular translocation of granules to the cell surface and transport of ions into the granules, resulting in granule solubility and mediator discharge.

Mediators

The activation and degranulation of mast cells causes the release of preformed, granule-associated (primary) mediators and the generation and release of unstored (secondary) mediators (Table 2). Table 2 denotes these mediators in terms of their functions, which include smooth muscle reactivity, chemotactic potential and enzymatic activity, and structural properties. The mediators have been best defined using rat mast cells, but in most instances human mast cells have proved similar.

Smooth muscle reactive mediators. Histamine, the decarboxylation product of histidine, is ionically bound to the proteoglycan-protein backbones of mast cell and basophil granules.[63] The sole mediator in this functional class preformed in human mast cells, it is displaced by sodium exchange in the extracellular fluid.[25] Histamine is catabolized by either oxidative deamination (histaminase) or by combined demethylation and oxidative deamination (histamine *N*-methyltransferase plus monoamine oxidase). The effects of histamine are expressed as constriction of smooth muscle and an increase in the distance between endothelial cells of venules, thereby increasing the potential for transudation of serum and for extravasation of leukocytes. The biologic activities of histamine follow its interaction with two specific classes of receptors on target cells. H_1 receptors predominate in skin and smooth muscle and are inhibited by classic antihistamines, whereas H_2 receptors are selectively blocked by burimamide, metiamide and cimetidine.[64] Pulmonary bronchoconstriction, vasodilation and increased cyclic guanosine monophosphate (cGMP) are H_1 receptor effects, whereas H_2 receptor effects include elevations in cAMP,[65] activation of human suppressor T lymphocytes[66] and inhibition of IgE-mediated basophil histamine release. The wheal-and-flare response to histamine in skin is due to a combined effect on H_1 and H_2 receptors.[67]

Slow-reacting substance of anaphylaxis is comprised of closely related products of the 5-lipoxygenase pathway of arachidonic acid metabolism termed leukotrienes C, D and E.[68,69] These compounds differ only in the amino acid constituents of a glutathione side chain. All are potent constrictors of peripheral airways smooth muscle; leukotriene D is the most active in this regard, and whereas both C and D are vasodepressors, leukotriene C constricts and D relaxes cutaneous vasculature.[69,70] Decreasing amounts of SRS-A are generated by increasingly pure human mast cell preparations, suggesting alternative sources of this class of mediator.[1] Such a source may be a human macrophage.[71]

Other products of arachidonic acid oxidation. Arachidonic acid mobilized from cell membrane phospholipids may be converted, via a cyclooxygenase-dependent pathway, to prostaglandins and thromboxanes, or by a 5-lipoxygenase enzyme to various hydroxyeicosatetraenoic acids and related compounds. The cyclooxygenase product prostaglandin D_2 has been generated by IgE-dependent activation of rat and human mast cells.[72] Other metabolites, including prostaglandins F_2 and E_2, have been identified after IgE-dependent activation of chopped human lung.[35] Animal and human smooth muscle is constricted by prostaglandins $F_{2\alpha}$ and D_2, thromboxane A_2, and both cyclic prostaglandin endoperoxides, G_2 and H_2, whereas prostacyclin (prostaglandin I_2) and prostaglandin E_2 relax smooth muscle. Following antigen challenge of sensitized guinea pig lung tissue, bronchoconstrictor metabolites of arachidonic acid predominate. In the skin, prostaglandin E causes a prolonged erythema.

Platelet-activating factor (PAF). [1-0-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine] is a unique phospholipid generated from rabbit but not human basophils by IgE-dependent mechanisms.[73] Its human source appears to be neutrophils and perhaps mast cells. Synthetic PAF is capable of inducing aggregation of human platelets and secretion of their serotonin. When injected into human skin, PAF causes local edema and erythema.[74] In animals PAF induces sequestration of platelets in lung tissue or skin and is a potent vasodepressor. Removal of platelets does not abrogate these effects of PAF.[75] In addition, in a platelet-dependent reaction PAF causes bronchoconstriction in animals.[75,76]

Serotonin is contained in human platelets, rather than mast cells or basophils, and may be released by the action of PAF. Whereas serotonin is capable of inducing vascular permeability in the

skin of rodents[77] and of contracting gastrointestinal smooth muscle,[78] it is ineffective as a constrictor of airways smooth muscle.

Chemotactic Mediators

Eosinophil chemotactic factor of anaphylaxis (ECF-A), the first mast cell-derived chemotactic factor described,[79] has been identified in anaphylactic supernatants of human lung mast cells, where it appears to be preformed,[1] and is released into the circulation of patients with experimentally induced urticaria (Table 3).[80,81] An acidic family of small peptides, ECF-A has been extracted from whole human lung tissue and structurally characterized from this source as two tetrapeptides with the sequence Val or Ala-Gly-Ser-Glu (valine or alanine-glycine-serine-glutamine).[82] This factor is preferentially chemotactic for eosinophils and deactivates them from further migration. A similar factor of greater hydrophobicity has been isolated from the serum of patients after experimental induction of cold urticaria (Figure 5).[83]

Intermediate molecular weight eosinophil chemotactic peptides. In addition to the low molecular weight, acidic ECF-A peptides, human lung and rat mast cells contain preformed and immunologically releasable chemotactic factors of molecular weight 1,500 to 3,000, with specificity for eosinophil polymorphonuclear leukocytes.[84,85] Factors of similar molecular weight and chemotactic specificity have been identified in the circulation of

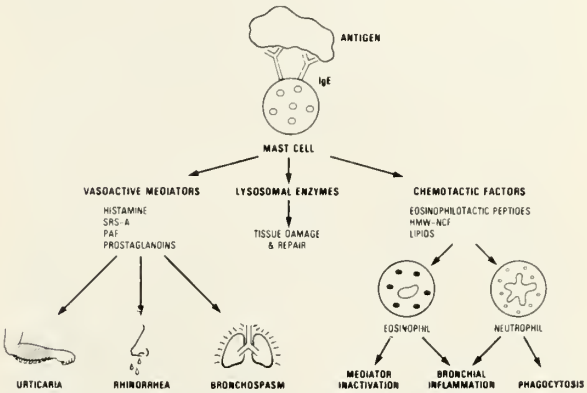

Figure 5.—Mast cell activation culminates in the release of three classes of chemical mediators that are partially responsiible both for allergic disease symptoms and the restoration of homeostasis. Abbreviations: HMW-NCF = high molecular weight neutrophil chemotactic factor; PAF = platelet-activating factor; SRS-A = slow-reacting substance of anaphylaxis.

TABLE 3.—*Chemotactic Mediators*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Eosinophil chemotactic factor of anaphylaxis (mast cells)	Preformed	Attract and deactivate eosinophils Increase eosinophil C_{3b} receptors	Glucocorticoids block effect Xanthines and β-agonists inhibit release
Eosinophil chemotactic factor oligopeptides (mast cells)	Preformed	Attract and deactivate eosinophils and mononuclear leukocytes (more acidic peptide)	Glucocorticoids block effect Xanthines and β-agents inhibit release
Neutrophil chemotactic factor (mast cells ?)	? Preformed	Attract and deactivate neutrophils	Glucocorticoids block effect Xanthines, β-agents and cromolyn inhibit release
Histamine	Preformed	H_1: Activation of directed and random migration of eosinophils H_2: Inhibition of directed and random migration of eosinophils and neutrophils	Classical antihistamine Cimetidine
Arachidonic acid metabolites			
Cyclooxygenase products HHT (many cell types)	Generated	Activation of directed and random migration of neutrophils and eosinophils	Aspirin and nonsteroidal antiinflammatory agents prevent generation
Lipoxygenase products HETE (many cell types)	Generated	Augmented random and directed migration of neutrophils and eosinophils	? Glucocorticoids prevent generation
Leukotriene B_4		Augmented random and directed migration of neutrophils and eosinophils	? Glucocorticoids prevent generation

HHT = 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid, HETE = hydroxyeicosatetraenoic acid.

patients following experimental induction of urticaria.[83]

High molecular weight neutrophil chemotactic factor (HMW-NCF). HMW-NCF has been described in human lung fragments and the sera of patients with urticaria[80,86] or asthma[82,87] following appropriate challenge. It has been characterized as a 750,000-dalton neutral protein that attracts and deactivates neutrophils. HMW-NCF is a sensitive marker for mast cell activation as it is present in sera of allergic asthmatic patients following challenge with doses of antigen insufficient to induce bronchospasm.

Lipid chemotactic factors. Chemotactic factors with specificity for both neutrophilic and eosinophilic polymorphonuclear leukocytes can be generated by lipoxygenase and cyclooxygenase-dependent pathways of arachidonic acid metabolism. The former pathway generates the HETE compounds (5,8,10,11- or 12-*L*-hydroxy-5,8,11,14-cicosatetraenoic acid) and leukotriene B_4 whereas the latter produces 12-*L*-hydroxy-5,8,10-heptadecatrienoic acid (HHT). These molecules have not yet been shown to be generated in immediate hypersensitivity reactions or by human mast cells. HETE molecules have an ECF-A-like spectrum of activity but enhance random migration and are less potent deactivators.[88] HHT has similar actions on neutrophils.[89] Leukotriene B appears to be a potent chemotactic and chemokinetic factor acting primarily on neutrophils.[90]

Other chemotactic factors. Activities directed toward lymphocytes have been reported to be observable in rat mast cells, whereas a chemotactic factor for mononuclear leukocytes is released into the circulation in cold urticaria.[83]

Granule-Associated Enzymes

Tryptase. A preformed tryptic protease termed tryptase is released following antigen challenge of IgE-sensitized human mast cells (Table 4).[91] This enzyme may cleave kininogen to yield bradykinin and to activate the Hageman factor..[92] The released kinins may contract smooth muscle, increase vascular permeability and induce pain. Activation of the Hageman factor could recruit the clotting, fibrinolytic and complement cascades. A potent chymotryptic enzyme termed chymase is present in rat mast cells, but is not found in human mast cells.

Other lysosomal enzymes. Myeloperoxidase, superoxide dismutase, arylsulfatase A and B, β-glucuronidase, hexosaminidases and aminopeptidase have been identified in isolated human or rat mast cells.[93] The function of these lysosomal enzymes remains speculative.

Structural Proteoglycans

Heparin, a sulfated, metachromatic mucopolysaccharide has been identified in mast cells from human lung.[94] Human heparin has a molecular weight of 60,000 and is comprised of a protein

TABLE 4.—*Enzymes and Proteoglycans*

Mediator and Source	*Preformed or Generated*	*Function*	*Therapeutic Inhibitor*
Tryptase (mast cell)	Preformed	Generate bradykinin Activate Hageman factor Proteolysis Degrade ground substance (?)	None
Arylsulfatase A (mast cell)	Preformed	Cleave sulfate esters Degrade ground substance (?)	None
Hexosaminidase (mast cell)	Preformed	Cleave hexosamines Degrade ground substance (?)	None
β-Glucuronidase (mast cell)	Preformed	Cleave glucuronide residues	None
Superoxide dismutase (mast cell)	Preformed	Cleave oxygen radicals	None
Myeloperoxidase	Preformed	Cleave hydrogen peroxide	None
Heparin (mast cell)	Preformed	Anticoagulation Bind to antithrombin III and platelet factor IV Inhibit complement activation Bind other preformed mediators	Protamine
Chondroitin 4 and 6 sulfates (basophils)	Preformed	Bind basophil mediators Bind to platelet factor IV	None

core to which are attached glycosaminoglycan side chains. Human heparin interacts with human antithrombin III to accelerate anticoagulation and may inhibit complement activation at several steps.[95] Basophilic leukocytes contain chondroitin sulfates rather than heparin as their granule-associated proteoglycan.

Mediator Interactions

The mediators of immediate hypersensitivity have been isolated, identified and characterized as individual factors, whereas immediate hypersensitivity syndromes reflect their combined interactions. Given the number of mediators, most have yet to be fully purified and there is little understanding of appropriate ratios of mediators generated or released in vivo.

The effects of histamine and SRS-A on smooth muscle are synergistic in vitro, and both histamine and SRS-A are known to cause prostaglandin generation. In addition, histamine may potentiate or inhibit ECF-A-induced eosinophil chemotaxis, depending on the ratio of individual mediators. These simple interactions suggest the many possible and potentially critical biological interactions yet to be elucidated. For example, the generation of PAF and SRS-A from neutrophils and mononuclear leukocytes suggests an important role for chemotactic mediators in regulating the availability of other crucial mediator-generating cells.

The Role of Mast Cells and Their Mediators in Tissue

The most direct evidence regarding the potential role of mast cells in inflammation has been generated in studies of human skin.[96,97] Using antibodies to IgE or antigen challenge of skin sites passively sensitized with pure IgE, it has been possible to discern several pathophysiologic consequences of mast cell activation. The initial event following mast cell activation is a pruritic wheal-and-flare reaction beginning in minutes and peaking 30 to 60 minutes after challenge. This reaction is characterized histologically by mast cell degranulation, endothelial activation and edema formation. After several hours the challenged site may become tender, erythematous and diffusely swollen. A biopsy specimen at this stage reveals the findings noted in the initial reaction, plus infiltration of neutrophils, eosinophils, basophils, lymphocytes and mononuclear leukocytes.[96,97] Often there are accompanying hemorrhage and fibrinoid vessel necrosis sufficient to warrant a diagnosis of necrotizing vasculitis.[96] These properties are certainly relevant to the allergic diseases, as discussed below, but may also be of great importance in homeostatic regulation at the host-environment interface. This latter speculation is strengthened by the fact that mast cells are found predominantly at this interface. Their homeostatic role may be related to removal of noxious particles, parasites and bacteria and in the regulation of the microvasculature.

Clinical Introduction

Although the mechanisms of mast cell mediator release and the structure and function of chemical mediators have been studied extensively in vitro, the role of mast cells in clinical disease is not as well defined. Because of their large number of IgE receptors and stores of chemical mediators of immediate hypersensitivity, one would expect mast cells to be crucial to the pathophysiology of allergic disease (Figure 5). The perception of the role of mast cells in disease has been based on histologic analysis showing mast cell degranulation, the identification of known mast cell products in biologic specimens or by the occurrence of signs and symptoms reproducible by specific mast cell mediators (Table 5). The following sections will attempt to clarify what is known about mast cells and their mediators in the pathogenesis of asthma, urticaria, angioedema, anaphylaxis and mastocytosis.

Asthma

Several types of pathologic and physiologic evidence show the importance of mast cells and their mediators in allergic asthmatic reactions. Mast cells can be found free in human bronchial lumina, in mucosa and submucosa of normal respiratory epithelium and in pulmonary secretions.[2,5] The density of mast cells increases as the airways become smaller, from 250 to 500 cells per cu mm in the trachea and bronchi and up to 1,000 cells per cu mm in more peripheral bronchioles.[98] In autopsies of patients with acute asthmatic attacks, mucous plugging, epithelial sloughing, smooth muscle hypertrophy, eosinophilia and occasional mucous gland hypertrophy are seen,[99] and the number of mast cells is diminished when compared with that of normal persons, presumably due to their degranulation.[100] This impression is supported by the finding that there are more degranulated mast cells in lung specimens

TABLE 5.—*Evidence Suggesting Mast Cell Participation in Disease*

Histologic evidence
Changes in mast cell numbers in tissues
Demonstration of mast cell degranulation
Presence of cells possibly recruited by mast cell mediators (eg, eosinophils, neutrophils)
Endothelial activation and disconnections
Biochemical evidence
Elevated levels of mediators in blood or secretions
Identification of mediators in tissue specimens
Specific IgE or antigen in blood or tissue
Clinical evidence
Signs and symptoms reproducible by mast cell mediators
Wheal-and-flare skin reaction
Pruritus
Bronchospasm
Rhinorrhea
Hypotension
Diarrhea
Pharmacologic agents that inhibit mast cell mediator release or mediator effects reduce symptoms
Antihistamines
Theophylline
Sodium cromolyn
β-Adrenergic agonists (?)

from persons with active asthma than in persons without asthma or with inactive asthma.[101] In sensitized dogs, challenge with appropriate antigens causes a decrease in airway mast cell numbers and in the content of lung histamine, whereas plasma histamine levels rise,[102] suggesting acute mast cell degranulation and release of mediators of immediate hypersensitivity. Humans suffering from acute antigen-induced asthma also have shown an augmentation of plasma histamine[103] and neutrophil and eosinophil chemotactic factor[87] levels from baseline, and patients with skin-test positive asthma have higher levels of histamine in their sputum than normal persons.[104]

The role of mast cells in nonallergic asthma is, however, less well defined. One hindrance to the elucidation of this role has been the difficulty in assessing small changes in plasma histamine. Fluorometric analyses are probably without validity in biologic fluid and only recently have adaptations of enzymatic histamine analysis proved sufficiently sensitive. With this technique, it has recently been shown that patients with exercise-induced asthma[105] and some patients inhaling methacholine[103] have rises in plasma histamine levels. Moreover, diurnal alterations in pulmonary function characteristic of some asthmatic patients parallel circadian changes in plasma histamine levels. Aspirin-induced asthma and cold-air induced bronchospasm, however, do not appear to be associated with appreciable mast cell mediator release.

Aside from direct measurements and observations, the prominent role of mast cells in asthma also has been implied by the pathophysiologic effects of its chemical mediators. Histamine constricts airway smooth muscle both by a direct local effect on irritant receptors[106] and by a reflex vagal pathway that can be blocked by atropine.[107] Histamine also increases the permeability of pulmonary venules, facilitating vascular protein leakage and edema formation.[108] Leukotrienes C, D and E (SRS-A) are potent bronchial smooth muscle constrictors preferentially acting on peripheral airway smooth muscle and also inducing edema formation.[109] These agents are 10-fold to 100-fold more potent on a weight basis than histamine in inducing bronchoconstriction. Prostaglandin D_2, formed by the metabolism of arachidonic acid via the cyclooxygenase pathway in mast cells, is another agent that constricts bronchial smooth muscle.[110] To date, however, there is no direct evidence that leukotrienes or prostaglandins are important mediators in human asthma. Platelet-activating factor, whose precise cellular source is unknown, appears during IgE-mediated reactions in which mast cells and basophils participate.[73] PAF induces bronchoconstriction in a platelet-dependent reaction that is associated with pulmonary platelet sequestration.[75,76] Such platelet sequestration and activation caused by PAF provides a source of platelet-derived mediators locally in lung tissue.

Finally, the effect of some pharmacologic agents in both ameliorating asthma and inhibiting mast cell activation suggests that mast cells are vital to asthmatic reactions. Theophylline, β-adrenergic agonists and sodium cromoglycate all inhibit histamine release from stimulated mast cells and decrease airways resistance in asthmatic patients, and are useful agents in the treatment of asthma.

The pathophysiology of the late phase of antigen-induced bronchospasm and the genesis of the bronchial hyperreactivity that is characteristic of asthma may also be due to mast cells. Late-phase reactions to allergen inhalation are seen as decreased pulmonary function occurring four to eight hours after antigen inhalation. Initially attributed to IgG immune complex reactions, these late reactions have been shown in skin to be clearly IgE mast cell mediated and associated with leukocyte infiltration and blood vessel damage.[97] As both early- and late-phase asthma are prevented

by pretreatment of patients with disodium cromoglycate,[111] whereas only the late phase is prevented by glucocorticoids,[112] it is reasonable to conclude that a mast cell-dependent inflammatory reaction is central to late-phase asthma. Of interest is that bronchoreactivity to histamine is altered in patients experiencing late-phase asthma but not in those in whom only the early phase can be identified.[113] It is presumed, therefore, that mast cell chemotactic factors and enzymes (see above) create an inflammatory substrate on which the chronicity of asthma may develop.

Urticaria and Angioedema

Urticaria is a raised, erythematous, blanching and pruritic cutaneous lesion similar to the wheal-and-flare reaction produced when histamine is injected into the skin. It may be IgE-mediated or associated with complement activation, immune complex reactions or caused by agents that induce mast cell degranulation directly and by agents that alter arachidonic acid metabolism.[114] Angioedema, a frequent companion of urticaria, is characterized by deep swellings that most commonly affect the face, lips, tongue, pharynx and extremities, but may occur in any area of the body. The disorders exhibit similar pathologic alterations in skin biopsy specimens, which reveal dilated microvasculature in the superficial and deep dermis, swollen collagen fibers and flattened rete pegs with occasional perivascular cellular infiltrates.[115,116] Mast cells are prominent in the normal dermis near vessels, nerves and hair follicles, with a density of approximately 7,000 cells per cu mm.[117] In urticaria, the mast cell density is probably normal, though some reports suggest an increase in mast cell numbers and the presence of mast cells in the epidermis.[118] Light and electron microscopy of urticated skin shows degranulating mast cells, evidence of endothelial activation and endothelial disconnections.[119] These latter findings are consistent with the known effects of histamine on the cutaneous vasculature.

Because they can easily be reproduced by specific stimuli, two types of urticaria, cold urticaria and cholinergic urticaria, have been studied extensively for the release of mast cell mediators into the circulation. Clinically, in patients with cold urticaria when exposed to cold air, cold water or ice, pain develops in the affected areas and on rewarming tingling, pruritus and wheaing develop. Persons with this disorder may have oropharyngeal edema after swallowing cold fluids.[120] Many patients with idiopathic cold urticaria have IgE capable of transferring cold responsiveness to normal skin.[120] In patients with cold urticaria challenged by immersion of one arm in an ice bath for three minutes prominent elevations in serum histamine concentrations develop and there are increased levels of three eosinophil chemotactic factors[80] and a single high molecular weight neutrophil chemotactic factor[86] in venous blood draining the urticated site. A biopsy specimen from these urticated areas shows mast cell degranulation.[121]

Cholinergic urticaria, a non-IgE-mediated disorder, may be provoked by a rise in the core body temperature due to pyrexia, warm baths or exercise. Cholinomimetic preparations injected intradermally produce a wheal-and-flare response in a third of these patients, and may induce smaller satellite lesions surrounding the original wheal, felt to be pathognomonic for cholinergic urticaria.[114] In nearly all such patients, this type of urticaria develops after warm baths or exercise and plasma histamine levels become elevated, as well as those of neutrophil and eosinophil chemotactic factors after experimental reproduction of their attacks.[122] Similarly, in a large group of patients with various forms of physical urticaria and idiopathic urticaria, suction blisters of lesional skin had increased content of histamine as compared with similar blisters on uninvolved skin.[123] Thus, release of mast cell mediators can be shown in both IgE- and non-IgE-mediated urticaria.

The cutaneous manifestations of histamine include an area of central erythema and edema formation (the wheal) with a surrounding flare or flush.[124] As little as femtomolar concentrations of histamine in the skin have been shown to cause pain and pruritus,[125] presumably acting through small nerve endings. Antihistamines, especially the H_1 receptor antagonists, have long been the mainstay of treatment of urticaria, though H_2 antihistamines may provide some added benefit. Other secondary mast cell mediators, including PAF, prostaglandins D_2 and E_2, leukotriene D and perhaps bradykinin, also increase vascular permeability and may produce wheal-and-flare responses when injected intradermally,[3] but their role in the development of urticaria is unknown.

Anaphylaxis

Systemic anaphylaxis is a life-threatening reaction often mediated by IgE and produced by

the actions of several chemical mediators on cardiovascular, cutaneous, respiratory and gastrointestinal target tissues. In IgE-mediated anaphylaxis, the reaction requires an initial exposure to an antigen, a latent sensitization period and subsequent reexposure to the antigen. Other anaphylactic reactions (sometimes called anaphylactoid) due to immune complexes, complement activation, direct mast cell degranulation and aspirinlike agents are clinically identical to anaphylaxis but occur on a nonimmunologic basis. Anaphylaxis is characterized by its effects on the noted target tissues and occurs as urticaria or angioedema, hypotension, cardiac arrhythmias, upper and lower respiratory tract obstruction, abdominal pain, vomiting and diarrhea, all of which may occur singly or in combination. Penicillin medications and hymenoptera stings are the most common causes of IgE-mediated anaphylaxis today, though horse serum provided most of the early examples. Radiocontrast media, aspirin and blood products provide most examples of non-IgE-mediated forms.

Clinical signs and symptoms usually develop within 30 minutes after exposure to the eliciting stimulus. A patient may notice first a tingling in the mouth or face, followed by warmth, flushing, pruritus and throat and chest tightness.[126] Bronchospasm, laryngeal edema, hypotension, vasomotor collapse and cardiac arrhythmias may ensue. Pathological findings correlate well with the clinical picture, such as pulmonary hyperinflation and edema, laryngeal edema, intraalveolar hemorrhage, bronchial hypersecretion, eosinophils in the bronchial walls and visceral congestion, though in some instances no pathological abnormalities have been identified.[126]

Although few studies of patients with active anaphylaxis have been done to identify the causative mediators, several mast cell and basophil-associated agents have been implicated in the pathophysiology of anaphylactic reactions. Histamine produces urticaria, angioedema, vasodilatation, hypotension, increased vascular permeability, vomiting and tenesmus[127] and is probably central in the pathogenesis of anaphylaxis. Leukotrienes are potent bronchial smooth muscle constrictors, some of which also increase vascular permeability and reduce pulmonary compliance in vivo.[70] Platelet-activating factor, another mediator generated by IgE-dependent mechanisms, causes local aggregation and degranulation of platelets and profound hypotension in animal models of anaphylaxis.[128] Eosinophil chemotactic factors may explain the tissue eosinophilia observed in anaphylaxis.

Rhinitis

Histologically a normal nasal biopsy specimen shows ciliated pseudostratified columnar epithelium, an underlying basement membrane, lamina propria, perichondrium and cartilage.[129] Small numbers of mast cells are present in the lamina propria near blood vessels and in loose connective tissue. Significantly, nasal mast cells are more abundant in nasal scrapings from persons with chronic allergic rhinopathy or nasal polyps[130]; however, there is little direct evidence proving the role of these cells in allergic or nonallergic rhinitis. Allergic persons do show elevated IgE levels in the nasal mucosa associated with hypereosinophilic nasal secretions.[131]

Evidence obtained in vitro suggests that in vivo when IgE bound to mast cells or basophils in the nasal mucosa interacts with extrinsic antigen, degranulation occurs followed by release of mediators of immediate hypersensitivity that act on nasal effector organs, namely blood vessels, goblet cells and mucosal glands. Clinical interaction with antigen results in swollen mucous membranes, nasal obstruction, hypersecretion, sneezing and itching, the classic symptoms of allergic rhinitis. That mast cell mediators are relevant to allergic rhinitis is attested to by the findings that histamine directly applied to the nasal mucosa produces an immediate profound rhinorrhea, dilating nasal blood vessels via H_1 receptors and increasing capillary permeability.[132] The presence of eosinophils suggests that ECF-A secretion from mast cells may be an important factor. The role of SRS-A and PAF in rhinitis is not known, and whether prostaglandins, which may either dilate or constrict nasal capillaries, have any clinical significance is uncertain. Essentially nothing is known about the role of mast cells in non-IgE-mediated rhinitis.

Many systemic or topical agents have been used to help ameliorate the symptoms of allergic rhinitis, with variable efficacy. Antihistamines administered orally are most often used to treat rhinorrhea and pruritus and are generally beneficial, especially in mild disease. Topically given disodium cromoglycate, perhaps by its effects on mast cell mediator release, has been useful in some

patients,[133] especially in those with eosinophilia on nasal smears.

Mastocytosis

Mastocytosis is an abnormal accumulation of mast cells in various tissues that can take several forms. The cutaneous form may be localized to a discrete area, often called a mastocytoma, or occur as a generalized involvement of the skin, urticaria pigmentosa.[134] Systemic mastocytosis almost always involves the skin, but mast cells may proliferate as well in liver, spleen, lymph nodes, the gastrointestinal tract, bone marrow, thymus and bone.[134] A third category of mastocytosis is mast cell leukemia, a very rare malignant form of mast cell proliferation.

Any type of mastocytosis is rare, occurring in 1 in 2,500 patients seen in a dermatologic clinic in one series.[135] The disease occurs most often in whites and usually has no identifiable hereditary component, though some family studies have described an autosomal dominant pattern of inheritance.[136] The purely cutaneous forms are most often seen in childhood and may wane with age, but 15 percent to 30 percent of those with skin involvement also have the systemic form of the disease, and this form predominates in adulthood.

The skin lesions of mastocytosis are classically reddish brown papules and plaques, primarily of the trunk, that urticate with contact (Darier's sign). Biopsy specimens of the skin lesions show large numbers of mast cells,[117] especially in dermis, generally clumped near small blood vessels and nerves. The concentration of histamine in the skin of patients with urticaria pigmentosa is five to ten times normal levels.[137]

The clinical features of mastocytosis may be attributed either to mast cell infiltration of tissues or to the pharmacologic effects of mast cell mediators on various organs. Mast cell infiltration of the liver or spleen may cause hepatomegaly or splenomegaly,[138] and rarely lymphadenopathy may result from the physical presence of mast cells in lymph nodes.[139] When mast cell infiltration of the bone marrow is pronounced, anemia or leukopenia may result, and mast cells may be present in the peripheral blood. The malignant form of this disorder, mast cell leukemia, said to occur in up to 4 percent of those with mastocytosis, but which certainly is much less common, is a rapidly fatal disease with total peripheral mast cell counts in the blood of 60,000 to 70,000 per cu mm.[139]

Mast cell proliferation in bone, best identified by technetium Tc 99m bone scanning, may show osteoporotic or osteosclerotic changes radiographically, and some patients with bony involvement have bone pain. Histamine is the predominant preformed mast cell mediator that produces clinical symptoms in patients with mastocytosis. Its release in the skin occurs as dermatographia, pruritus, urticaria and flushing.[124] The latter symptoms and associated hypotension may be due not only to histamine, but also to the mast cell metabolite of arachidonic acid, prostaglandin D_2. Although the symptoms of mastocytosis generally occur without clear-cut precipitating events, the ingestion of alcoholic beverages may trigger acute symptoms,[140] presumably through a histamine-release phenomenon. Such acute episodes may at times be confused with anaphylaxis. The gastrointestinal manifestations of histamine excess include nausea,[141] diarrhea, steatorrhea, malabsorption, peptic ulcer disease and gastrointestinal bleeding,[142] which may be aggravated by release of heparin from mast cell granules.[143] When mast cell proliferation in the nose is prominent, histamine may contribute to a pronounced rhinorrhea.[139] Other symptoms thought to be due to high circulating levels of histamine include palpitations, tachycardia, malaise, headache, cognitive disorganization and bronchospasm.[139] These signs and symptoms may be confused with those of the carcinoid syndrome but, as seen in Table 6, the different mediators produce different clinical and laboratory findings.

Hematologic findings may relate to other mast cell constituents. Mast cells contain factors chemotactic for eosinophils that may contribute to the peripheral blood eosinophilia seen in some patients with mastocytosis.[144] A prolonged partial thromboplastin time in other patients with mastocytosis has been attributed to the release of heparin from mast cell granules.[139] Some patients may also have hypocholesterolemia, possibly due to heparin's effect on cholesterol metabolism.[144]

In the past, the mainstay of treatment for mastocytosis had been antihistamines. Even with the advent of both H_1 and H_2 receptor blockers, only partial relief of symptoms has been obtained with these drugs. Because of the presence of increased amounts of prostaglandin D_2 metabolites in the urine of patients with mastocytosis, aspirin therapy has been used for this disorder[141] and may partially ameliorate symptoms, particularly hypotension, while decreasing the amounts of urine prostaglandin D_2 metabolites. Oral adminis-

TABLE 6.—*A Comparison of Mastocytosis and Carcinoid Syndrome*

Clinical Findings	*Description*	
	Mastocytosis	*Carcinoid*
Urine content	Histamine	Serotonin
Skin lesions	Urticate	Pellagra-like
Flush appearance	Red	Cyanotic
Duration of flush	30 Minutes	10 Minutes
Pruritus	Present	Rare

tration of sodium cromoglycate, a drug felt to stabilize mast cell membranes and thereby inhibit mediator release, has been shown to significantly decrease subjective symptoms.[145] In one case report, a single dose of mithramycin alleviated pain caused by mast cell infiltration of bone.[146]

Conclusion

Mast cells are uniquely positioned at sites of host-environment interactions, armed with receptors for IgE and other secretagogues and loaded with a supply of potent biologically active mediators. They thus may play a role in homeostatic regulation of the host-environment interface. In addition, these properties of mast cells enable them to participate in processes perceived as disease rather than homeostasis. Such disorders include the family of allergic diseases (asthma, rhinitis, urticaria) and nonallergic problems as well. In fact, the recruitment of mast cells in non-IgE-mediated processes may well be an important and often overlooked pathophysiologic sign of diseases as varied as cystic fibrosis, ulcerative colitis and neoplasia. Only as histopathologic assessment of disease focuses on mast cells and the biochemical identification of mast cell mediators is refined can the understanding of the role of this cell proceed from speculation to knowledge.

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Specialty Conference

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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington, Seattle. Taken from a transcription, it has been edited by Drs. Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor of Medicine and Chairman of the Department of Medicine.

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Recent Developments in the Diagnosis and Treatment of Urinary Tract Infections

WALTER E. STAMM:* In the past few years, several well-established principles in the diagnosis and treatment of urinary tract infections (UTI) have been challenged. New diagnostic tests have emerged, the utility of older tests has been questioned, changing antibiotic sensitivity patterns of urinary pathogens have been documented, the role of *Chlamydia* and staphylococci in causing urinary infection has been better defined and recent data have given rise to debate over selection of antimicrobial agents and duration of therapy. In addition, the role of prophylactic antibiotic therapy in patients with recurrent urinary tract infections has been further studied, both with respect to cost considerations and clinical effectiveness. In light of these recent developments, a review of selected aspects of the care of patients with urinary tract infections seems warranted.

The Meaning of Significant Bacteriuria

To most physicians a culture of a clean-catch midstream urine specimen that grows more than 100,000 colonies per ml confirms a diagnosis of urinary tract infection, and a culture growing fewer than 100,000 colonies per ml makes the diagnosis unlikely. This diagnostic criterion arose from the classic studies of Kass[1,2] and Sanford.[3] They showed that over 95 percent of women with acute pyelonephritis have 100,000 or more bacteria per ml of urine and that this number of microorganisms, when found in two or more consecutive cultures, reliably distinguished infection from contamination in women who had asymptomatic bacteriuria. Most women seen by physicians for UTI, however, have acute symptomatic infection confined to the lower urinary tract, rather than acute pyelonephritis or asymptomatic bacteriuria. Using the 100,000 colonies per ml diagnostic criterion for infection in these patients has been less satisfactory. In one study of 130 women with an acute onset of dysuria and frequency, for example, only 56 actually had more than 100,000 colonies per ml on cultures of urine specimens, whereas 41 had sterile urine cultures and 33 had counts of fewer than 100,000.[4] Similar data in other studies[5-8] led to the concept that women whose midstream cultures grew fewer than 100,000 organisms per ml did not have UTI but suffered instead from the urethral syndrome. Because the pathogenesis of this syndrome was unclear, most women with urethral syndrome were not treated with antimicrobial drugs. Later, however, studies using suprapubic aspiration showed that nearly a third of symptomatic patients with low coliform counts in voided urine specimens also had coliform bacteria in their bladders.[9,10]

A recent Seattle study has provided information relevant to the interpretation of bacterial colony counts in midstream urine specimens obtained from symptomatic patients.[11] Of 181 women who came to an outpatient clinic with acute dysuria and frequency, 102 had counts of 100,000 per ml or more, but 79 had fewer than 100,000 colonies per ml. Women with evidence of upper urinary tract infection, vaginitis or herpes simplex virus infection were excluded from this study. In all, 56 of the 79 women with fewer than 100,000 colonies

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ABBREVIATIONS USED IN TEXT

ACB = antibody-coated bacteria
IVP = intravenous pyelography
STD = sexually transmitted disease
UTI = urinary tract infections

per ml in a midstream urine specimen participated in the study and 27 had suprapubic aspirates that grew *Escherichia coli, Klebsiella* sp or staphylococci. In addition, cultures of urethral and vaginal specimens were obtained from all study patients, and the same high rates of *E coli* carriage in the urethra (78 percent to 84 percent) and vagina (79 percent to 92 percent) were found both in women with 100,000 or more organisms per ml and in those with low coliform counts in midstream urine specimens, but not in women without symptoms. These data suggested that the pathogenesis of infection in the group with low coliform counts in a midstream urine specimen may be similar to that in the group with 100,000 colonies per ml or more; that is, ascending infection probably occurs in both groups, ultimately resulting in cystitis. Indeed, the clinical presentation of patients with 100,000 or more colonies per ml in midstream urine specimens could not be distinguished from those with fewer than 100,000 colonies per ml. Approximately half of each group exhibited gross or microscopic hematuria (or both), essentially all women in both groups had pyuria and women in both groups typically described a sudden onset of illness that began three to four days before being seen in clinic.

In summary, data now available suggest that symptomatic coliform infection of the bladder and urethra will not, in many women, be accompanied by midstream urine specimens that grow 100,000 colonies per ml or more on cultures. Clinicians and microbiologists must, therefore, reconsider the interpretation of culture results of midstream urine specimens. Further studies are urgently needed to more clearly define the sensitivity and specificity of quantitative criteria for infection in patients with lower urinary tract infection. Until these become available, clinicians and microbiologists must be aware that midstream urine specimens growing fewer than 100,000 bacteria per ml on culture can have diagnostic importance.

The Meaning of Pyuria

Although many experts have criticized using analysis of urine for diagnosing urinary tract infections, most physicians still place importance on the number of leukocytes in the urinary sediment. Unfortunately, measurement of pyuria by examination of the urinary sediment as practiced in most hospitals lacks precision. By this method, an unknown quantity of urine is centrifuged for an approximate period, and an unknown dilution of the sediment is then examined. In studies where pyuria has been more precisely measured, it has been found in nearly all women with acute UTI. Mabeck[12] showed that an elevated leukocyte excretion rate in the urine correlated with acute symptomatic UTI; most normal persons excrete less than 400,000 leukocytes an hour, while more than 95 percent of patients with acute symptomatic infection are well above this level.

A simpler and highly reproducible method of measuring pyuria has been described.[13] In this technique, leukocytes per cubic millimeter of urine are determined by examining a fresh, uncentrifuged specimen in a hemacytometer chamber. This method correlates well with the leukocyte excretion rate and can be done easily in a clinical setting. By hemacytometer determination, most asymptomatic women with sterile urine have fewer than eight leukocytes per cu mm in their midstream urine specimens. In contrast, nearly all patients with acute cystitis characterized by bacteriuria of 100,000 or more per ml have more than eight leukocytes per cu mm and most have more than 60 per cu mm. Patients with the acute urethral syndrome may be divided into those with or without eight or more leukocytes per cu mm of urine. In the Seattle study, 85 percent of patients with pyuria had a proved infection (coliform, staphylococcal, or chlamydial) and patients without pyuria usually had no demonstrable infection.[11] All patients positive for bacteria on suprapubic aspirate cultures and most patients positive for *Chlamydia* sp on cultures had pyuria with counts well above eight leukocytes per cu mm. Thus, careful measurement of pyuria in patients with urinary tract symptoms can be helpful in separating patients who will have proved infection from those who will not.

Antibody-Coated Bacteria Test

A relatively new diagnostic test, the antibody-coated bacteria (ACB) assay, has been proposed as a noninvasive, inexpensive and apparently accurate means of identifying the site of UTI. The ACB test uses a fluorescence assay to detect immunoglobulin on the surface of bacteria in the

TABLE 1.—*Studies Comparing the Antibody-Coated Bacteria (ACB) Test With Direct Localization Procedures*

Study	Patients	Method	Results of ACB: Sensitivity number (percent)	Results of ACB: Specificity number (percent)
Jones et al, 1974[14]	26	Bladder washout	17/18(94)	8/8 (100)
Kohnle et al, 1975[18]	26	Bladder washout	18/18(100)	8/8 (100)
Hawthorne et al, 1978[20]	31	Ureteral catheterization	16/16(100)	10/15(67)
Riedasch et al, 1978[17]	134	Ureteral catheterization	36/50(72)	59/84(70)
Harding et al, 1978[19]	51	Bladder washout	31/37(84)	14/14(100)

urine. Early studies suggested that upper urinary tract infection was characterized by the presence of ACB in urinary sediment and lower urinary tract infection by its absence.[14,15] However, only a few studies have directly compared the ACB test with either ureteral catheterization or the bladder washout localization technique and, unfortunately, many of the patients in these studies were on urologic services and had chronic UTI (Table 1).[14,16-20] Further experience comparing the ACB test with direct localization procedures in acutely symptomatic younger women is still needed.

An interesting epidemiologic observation has been the variability in the percentage of women with positive ACB tests, depending on the population being studied. In a cooperative study involving Parkland Memorial Hospital in Dallas, the Kaiser-Permanente Hospital in Portland and the Massachusetts General Hospital in Boston, the percentage of women having only lower urinary tract symptoms but positive results on ACB assay ranged from 63 percent at Parkland to 8 percent at the Kaiser-Permanente Center.[21] The authors speculated that this difference might relate to health-care-seeking behavior, with some patients who had only mild symptoms obtaining care early in the course of infection, and others waiting until more severe symptoms develop before going to the hospital. Rates of positive findings on ACB test in Seattle range from 13 percent at the student health clinic at the University of Washington to nearly 50 percent at the sexually transmitted disease (STD) clinic at Harborview Medical Center. These data show a gradation similar to the findings of Rubin and colleagues[21] and may also be related to the availability of care.

False-negative and false-positive results occur with the ACB test. False-negative tests usually result from a delayed or inadequate antibody response. In animal models, an infection must be established for 10 to 14 days to stimulate a sufficient immune response for the ACB test to become postive.[22] Most women with a first infection will receive treatment before the development of antibodies against their infecting strain. In a study by Rubin and co-workers,[21] the average duration of symptoms in ACB-negative patients was two days, compared with six days in ACB-positive patients. In a Scandinavian study,[23] the percentage of patients with positive ACB assays was greater among those with recurrent infections or with a long duration of illness than in patients with first infection. These studies, like the animal models, suggest that sufficient time for an immune response to develop is necessary before the ACB test becomes positive. False-negative results with the ACB test may also be seen in patients with infections characterized by fewer than 100,000 bacteria per ml. Presumably, there are insufficient bacteria to bind antibody, leading to a false-negative result in these patients.[24]

False-positive results on ACB tests occur for several reasons. Vaginal or fecal strains of *E coli* may be antibody coated and can contaminate urine specimens. Other tissue infections, primarily prostatitis and hemorrhagic cystitis, may result in antibody production and lead to a positive result. In addition, certain microorganisms (*Pseudomonas,* staphylococci and yeasts) often produce false-positive findings.[14]

Uncertainty concerning the specificity and sensitivity of the ACB test has led most investigators to recommend that it be reserved for epidemiologic and investigative purposes and not be used clinically at this time.

The Role of Cystoscopy and Intravenous Pyelography

Three recent studies have raised important questions about the routine use of intravenous pyelography (IVP) and cystoscopy in women with recurrent urinary tract infections (Table 2).[25-27] All three studies examined women with recurrent, acute lower urinary tract infections and excluded patients with known upper urinary tract surgical procedures, renal calculi, anatomic abnormalities

TABLE 2.—*Role of Intravenous Pyelography (IVP) in Women With Recurrent Urinary Tract Infection*

Method	*Fair et al, 1979*[25] *Questionnaire*	*Engel et al, 1980*[26] *Retrospective Record Review*	*Fowler & Pulaski, 1981*[27] *Prospective Study*
Women studied	164	153	104
IVP normal	144	136	87
Anatomic variant ..	11	9	6
IVP abnormal	9	8	11
Correctable	0	0	0

or relapsing infections. In the three studies, 80 percent to 85 percent of women had completely normal IVP's despite a history of two to three UTI's per year. Anatomic variants probably unrelated to infection were found in 6 percent to 8 percent. IVP abnormalities that could have been related to infection were found in 6 percent to 8 percent, but none of these abnormalities were considered correctable by the authors. Thus, none of the 421 patients had their treatment altered on the basis of an IVP. Similarly, cystoscopy rarely showed a correctable lesion: of 153 women studied, four had potentially correctable lesions (one patient with a colovesical fistula and three with urethral diverticula).[25-27]

Given the apparent low yield of IVP in women with recurrent UTI, the risks and benefits of the procedure should be carefully weighed. Important adverse reactions to IVP include minor skin reactions (1 in 100 patients), major vasomotor phenomena (1 in 1,000) and death (1 in 10,000 to 25,000). Furthermore, IVP's generally cost at least $110. An IVP appears to be most useful in patients with a history of childhood urinary tract infections, possible nephrolithiasis, relapsing infection or painless hematuria, but not in women with uncomplicated lower urinary tract infections.

Treatment of Urinary Tract Infection

Continuing emergence of antibiotic-resistant microorganisms has complicated the treatment of urinary tract infections. In Seattle microorganisms causing UTI in patients seen at the STD clinic at Harborview Medical Center, the student health clinic at the University of Washington and the Public Health Service Hospital frequently show in vitro resistance to ampicillin (20 percent to 25 percent), tetracycline (35 percent to 40 percent) and sulfa drugs (20 percent to 25 percent). Of the drugs routinely used for outpatient treatment of UTI, only trimethoprim-sulfamethoxazole was effective in vitro in over 95 percent of patients. In vitro resistance, however, does not necessarily imply that a drug cannot be successfully used to treat urinary infection. Urinary concentration of many antimicrobial medications may allow successful treatment of microorganisms judged resistant on the basis of in vitro testing.

In recent years, the duration of antibiotic therapy for urinary tract infection has been reconsidered. ACB testing, which may permit noninvasive identification of the site of infection in treatment studies, has been used to examine the feasibility of single-dose therapy of acute lower urinary tract infections.[28] The rationale for single-dose therapy stems from several considerations. First, histopathologic studies in which biopsy specimens of the bladder are taken show that acute cystitis is a superficial infection that does not extend beyond the mucosa in most cases.[29] Second, many clinicians have inadvertently seen single-dose therapy work when a patient with acute cystitis for whom ten days of antibiotic therapy was prescribed, feels better after one day of treatment and stops taking the medication. When seen for test of cure two weeks later, the patient has sterile urine. Third, physicians in STD clinics routinely use single-dose therapy for other genital mucosal infections, specifically gonococcal urethritis and cervicitis. Finally, the bladder washout procedure, which involves installation of antibiotics into the bladder, cures approximately 30 percent of patients with cystitis.[30]

Fang and co-workers[28] described the first clinical trial of single-dose therapy in patients who had a negative ACB test. All 22 patients who had lower urinary tract infection as judged by the ACB test were cured by a single 3-gram dose of amoxicillin given by mouth. Patients with a positive ACB test were treated only with a conventional ten-day course of amoxicillin and 50 percent failed to improve on this therapy. Subsequently, other studies using several different antibiotic drugs have confirmed the efficacy of single-dose therapy in an ACB-negative patient (Table 3), achieving cure rates of 68 percent to 100 percent.[31-36]

It should be emphasized that most single-dose antibiotic studies have examined patients with a negative result on ACB test and an infecting microorganism that was sensitive to the antibiotic being used. Developing general recommendations for practicing clinicians based on these studies is complicated by their preselected nature. If an ACB test is not available and the sensitivity of the in-

TABLE 3.—*Recent Trials of Single-Dose Therapy Using Antibody-Coated Bacteria (ACB) Localization*

Study	*Drug*	*Dose*	*Efficacy**	*Relapse*†	*Reinfection*†
Fang et al, 1978[28]	Amoxicillin trihydrate	3 grams	22/22	0	2
Rubin et al, 1980[21] ...	Amoxicillin trihydrate	3 grams	34/38	0	1
Counts et al, 1982[33] ..	TMP-SMX	160 to 800 mg	36/38	3	6
Ludwig et al, 1980[31] ..	TMP-SMX	160 to 800 mg	18/19	0	1
	TMP-SMX	320 to 1,600 mg	19/20	0	2
	Sulfisoxazole	1 gram	17/20	0	1
	Sulfisoxazole	2 grams	15/17	0	2

TMP-SMX = trimethoprim-sulfamethoxazole.

*Eradication of infecting strain and symptoms at three to seven days' follow-up evaluation.
†At two to six weeks' follow-up evaluation.

fecting organism is unknown, as is usually the case in clinical practice, single-dose therapy poses several potential problems. Antimicrobial resistance may be more important when using single-dose therapy than with the conventional ten-day course. With conventional therapy, urinary tract infections can often be treated with antibiotics to which the organism is resistant in vitro, probably due to the high urine-to-serum concentration ratio (often 10:1) that many antibiotics achieve. As yet, the clinical efficacy of single-dose therapy in patients whose organism exhibits in vitro resistance has not been extensively studied. The effects of single-dose therapy on vaginal coliform colonization and long-term recurrence rates also deserve further study. Preliminary data suggest that single-dose therapy may be less efficacious than a ten-day course in eradicating vaginal coliforms[33]; failure to eliminate coliforms from the vaginal and urethral reservoir might result in more rapid recurrences. Finally, studies comparing different single-dose regimens and regimens of three to five days should be done in an effort to determine the optimal treatment for patients with dysuria and frequency.

Despite these uncertainties, single-dose therapy assures compliance, costs less than conventional therapy and causes fewer side effects. Even without the ACB test, physicians should consider single-dose therapy in adult women who have acute onset of lower urinary tract symptoms, no upper urinary tract signs, an illness of less than seven days' duration and where reasonable follow-up for a test-of-cure culture can be assured.[36] The clinical setting should not be a "high positive ACB population," such as a city hospital emergency room. Pregnant women and diabetic patients should not be treated with single-dose therapy until trials have been carried out on these types of patients.

Antimicrobial Prophylaxis for Recurrent UTI

Antimicrobial prophylaxis reduces the number of recurrences that develop in an infection-prone patient per year.[37] In Seattle studies 80 percent of infection-prone women given a placebo had a recurrent infection within six months, whereas administration of trimethoprim-sulfamethoxazole (half a tablet a day), nitrofurantoin (100 mg a day), or trimethoprim alone (100 mg a day) reduced the infection rate to near zero.[38] Unfortunately, the beneficial effect of antimicrobial prophylaxis does not continue after the patient stops taking the drug; as soon as prophylaxis is withdrawn, the infection rate returns to the baseline level. Studies to date have shown no significant emergence of resistant organisms in patients given long-term antimicrobial prophylaxis, and when recurrent infections have developed after stopping the antibiotic medication, the organisms identified have usually been sensitive to the agent previously used.

Who should receive antimicrobial prophylaxis and for how long? Our experience suggested that patients tend over many years to have a baseline pattern of recurrent infections that is predictable.[39] Most patients who have more than two infections per year appeared to benefit from long-term prophylaxis by reduced morbidity. In Seattle the cost of daily prophylaxis approximates $85 per patient per year, whereas the cost of three to four infections per patient-year exceeds $400.[40] Thus, prophylaxis appears cost effective in women with annual recurrence rates of three infections or more.

Prophylactic regimens of antibiotic medication taken daily, thrice weekly or after sexual intercourse all effectively prevent recurrent infections,[37] but deciding how long to give prophylaxis is difficult. An initial six months of prophylaxis should

be given to determine tolerance and effectiveness. Thereafter, knowledge of a woman's baseline rate of infection provides the best guide to need for longer prophylaxis. Many women with baseline infection rates of one to two a year may do well with three to six months of prophylaxis. Most women with three or more infections a year over many years will simply return to this baseline infection rate after discontinuation of prophylaxis and should be considered candidates for long-term prophylaxis.

Relationship of Sexual Activity to UTI

The epidemiologic observation that UTI's recur most frequently in young, sexually active women suggests a possible role of sexual activity in the pathogenesis of these infections. For *E coli* infection, however, there is little evidence supporting actual venereal passage of strains from a sexual partner. More likely, women in whom persistent coliform colonization of the periurethral area develops may be at increased risk of infection when they have regular sexual activity because urethral massage associated with intercourse facilitates entry of microorganisms into the bladder.[40-42] The successful use of postcoital prophylactic antibiotic therapy to prevent recurrent UTI supports this hypothesis.

Sexual transmission of urethral pathogens can produce dysuria and frequency, indistinguishable from coliform infection. Recent studies strongly suggest that among young, sexually active women, chlamydial infection causes the acute urethral syndrome.[11] Chlamydial infection in such women is characterized by dysuria, urinary frequency, sterile pyuria and response to treatment with tetracyclines.[11,43] *Staphylococcus saprophyticus,* a urinary pathogen responsible for about 10 percent of acute, symptomatic lower urinary tract infections in college women in Seattle, may also be sexually transmitted, but further study of this organism must be undertaken to substantiate this hypothesis.

Clinical Approach to Women With Acute Dysuria and Urinary Frequency

The newer concepts outlined can be incorporated into a revised clinical strategy for women with acute dysuria and urinary frequency (Figure 1). In a patient with lower urinary tract symptoms and signs, a diagnosis of vaginitis should be considered first. Factors favoring this diagnosis include an associated history of recently increased or changed vaginal discharge, vaginal odor, vaginal or labial itching or previous recurrent vaginitis. In most instances, women with vaginitis as the cause of dysuria have external symptoms, that is, burning as urine passes over the labia. They generally do not have associated symptoms of urinary urgency or frequency, suprapubic pain or hematuria. In sexually active women with dysuria and any of the historical factors noted above, a pelvic examination should be done and potential causes of vaginitis evaluated by physical examination, determination of vaginal fluid pH and wet smear (prepared with 0.9 percent sodium chloride solution) and potassium hydroxide (KOH) microscopy. Whether a vaginal examination should be done in all women with dysuria remains debatable. Komaroff and colleagues[44] suggested that in women with internal dysuria and none of the above-mentioned symptoms suggesting vaginitis, a pelvic examination was rarely helpful and could be omitted. However, because sexually transmitted pathogens such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are prominent causes of dysuria, a strong argument can be made for doing a vaginal examination in all sexually active women with acute dysuria and urinary frequency.

After excluding vaginitis, a clinician should consider the two other causal categories, namely, urethritis-causing pathogens *(C trachomatis* and *N gonorrhoeae)* and urinary pathogens (coliforms and *S saprophyticus*). Although these two groups cannot be clearly distinguished on clinical grounds alone, suprapubic pain, gross hematuria or a history of UTI suggests the latter group.[11] In these women, abrupt onset of symptoms generally occurs and the patients have usually experienced symptoms for only one to four days before seeking medical care. Laboratory data consistent with coliform infection include the presence of pyuria on examination of a clean-voided, midstream, uncentrifuged urine specimen (more than eight leukocytes per cu mm when examined in a hemacytometer chamber), accompanied by hematuria in about 50 percent of cases.[11] When coliforms or staphylococci are present in bladder urine in quantities of more than 100,000 bacteria per ml, they can be readily seen in a Gram stain of unspun urine, confirming the diagnosis. However, if these agents are present in lesser quantities, the Gram stain will be negative and the organism identified only by culture.

Infection with *C trachomatis* or *N gonorrhoeae* occurs most commonly in young, sexually active

women who have had a recent sex partner change. A history of a partner with recent gonococcal or nongonococcal urethritis may also be obtained. Women with acute dysuria and urinary frequency due to chlamydial infection usually do not have symptoms of urgency, hematuria or suprapubic pain and give a history of a gradual onset of illness and 7 to 21 days of symptoms before seeking medical attention.[11] Pelvic examination may show mucopurulent cervicitis and many polymorphonuclear leukocytes but no gonococci on Gram stain of a cervical smear. Urine analysis shows pyuria (defined above), no hematuria and no bacteria on Gram stain of an unspun urine specimen. A Gram stain of a urethral smear will frequently show leukocytes. Women with gonococcal urethritis or cervicitis, or both, also tend not to have suprapubic pain or hematuria but may exhibit an illness of more abrupt onset. A Gram stain of a cervical smear will show intracellular Gram-negative diplococci in about 50 percent of women and, as with a chlamydial infection, pyuria should be seen. However, it must be emphasized that laboratory values for the diagnosis of urethritis due to *Chlamydia* or gonococci in women have not been as well studied as in men. The less precise measurement of pyuria in a centrifuged urine specimen examined under a coverslip, as done in most routine hospital laboratories, may be less useful in separating infected and uninfected patients. Gram stain of urethral smears in women needs further evaluation.

In cases not due to vaginitis, final diagnostic confirmation usually requires culture. The urine will reveal coliforms or staphylococci in quantities greater than 100,000 bacteria per ml in women with acute cystitis. Care should be taken to be certain the laboratory does not disregard *S saprophyticus,* a coagulase-negative *Staphylococcus,* as a contaminant. In women with a clinical presentation typical of cystitis but with 100 to 10,000 coliforms or staphylococci in a midstream urine

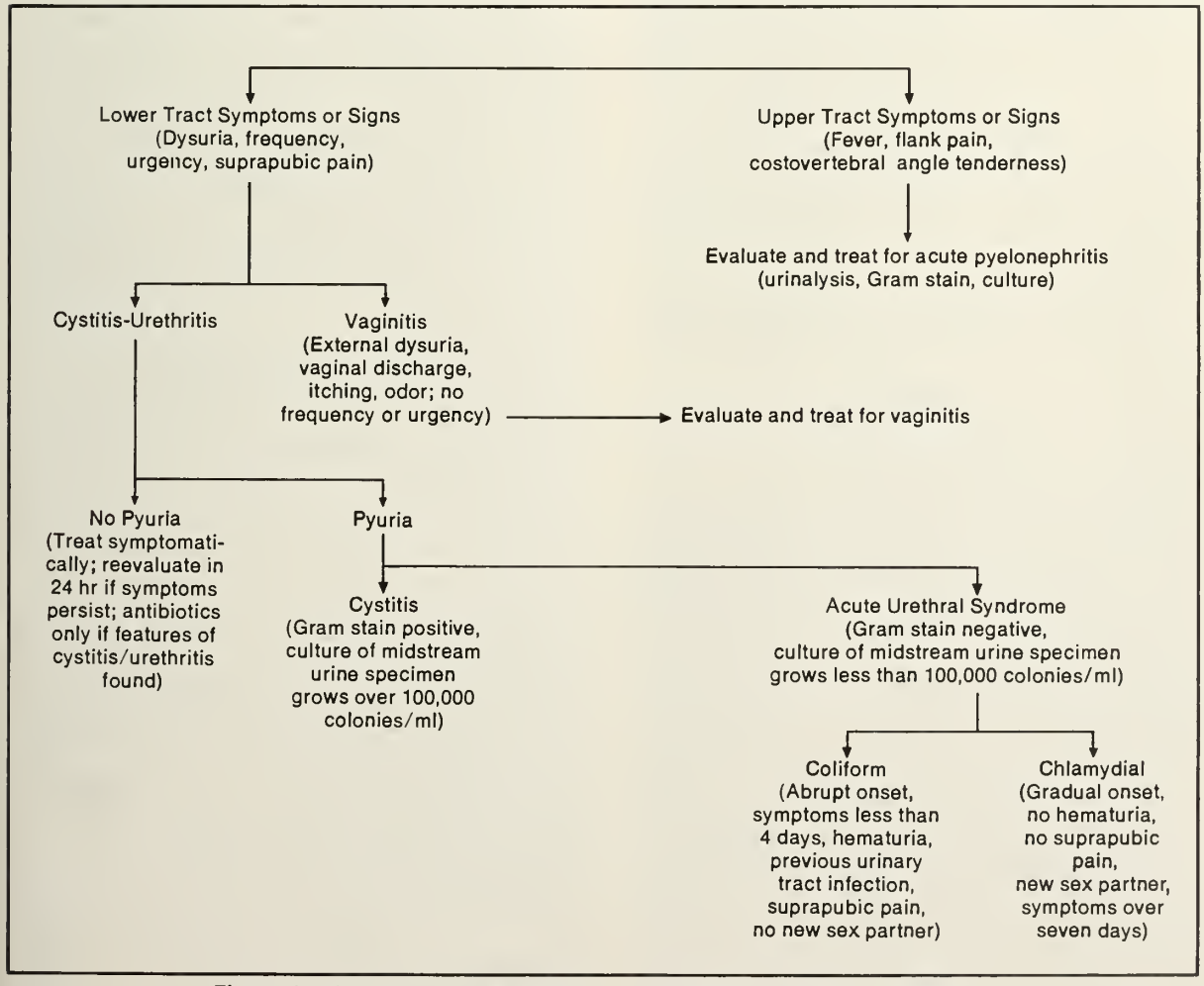

Figure 1.—Approach to the diagnosis of dysuria and urinary frequency.

specimen, there is a strong indication of a diagnosis of acute urethral syndrome. Particular care should be exercised to obtain clean-voided specimens in these patients to minimize contamination of the cultured urine with low quantities of perineal or fecal coliforms. In some patients, specimens obtained by urethral catheterization or suprapubic aspiration may be the only means of accurately distinguishing "low count" coliform infection from a contaminated specimen.

If available, chlamydial cultures of both urethral and cervical specimens should be obtained in women with sterile pyuria. A thin, calcium-alginate swab should be used for the former and a plastic-shafted swab for the latter, with care taken in both cases to obtain many epithelial cells. In instances where chlamydial cultures are not available, a tentative diagnosis of *C trachomatis* infection can be made by finding sterile pyuria (that is, pyuria associated with neither coliforms nor *S saprophyticus*), a culture negative for gonococci and clinical features of chlamydial infection, including dysuria and urinary frequency. Chlamydial infection can be effectively treated with a 10- to 14-day course of tetracycline, erythromycin or trimethoprim-sulfamethoxazole.[43] It should be emphasized, however, that simultaneous infection with more than one agent may occur, and all appropriate cultures should be obtained if possible.

In women without demonstrable pyuria, an infectious agent responsible for acute dysuria and frequency usually has not been found.

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Clinicopathologic Conference

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Refer to: Bachhuber R, Fitchen JH, Harty-Golder B: Rash and eosinophilia in a 23-year-old man, Oregon Health Sciences University (Clinicopathologic Conference). West J Med 1982 Sep; 137:221-227

Rash and Eosinophilia in a 23-Year-Old Man

RAY BACHHUBER, MD:* A 23-year-old white man was transferred from the Oregon State Correctional Institute for evaluation of possible vasculitis. He had served five years of a ten-year sentence for armed robbery. Seven months before admission a purple, confluent rash developed on his hands and feet with associated edema and pain. Arthritis of the small joints of the hands and an episode of hematochezia were also noted. Six months before admission an episode of "pneumonia" developed with severe pleuritic chest pain and a productive cough. A complete blood count (CBC) at that time showed a leukocyte count of 27,300 per cu mm with 82 percent segmented forms and 16 percent lymphocytes; no eosinophils were noted. He was treated with antibiotics and gradually improved. Findings on an x-ray film of the chest made three weeks after the episode of "pneumonia" were unremarkable.

Four months before admission the areas of rash ulcerated and became more swollen and painful. Several antibiotic preparations given orally were tried but produced no improvement. His arthritis worsened and the arthralgias spread to several large joints. Three months before admission, prednisone therapy at a dosage of 50 mg twice a day was started; rapid improvement in the arthritis and some improvement in the rash occurred. Over the next four weeks the prednisone dosage was rapidly tapered to 5 mg a day. Six weeks before admission his rash and arthritis flared and the prednisone dosage was increased to 20 mg a day without effect.

A week before admission the patient felt that his condition was deteriorating while receiving prednisone, trimethoprim-sulfamethoxazole and triamterene-hydrochlorothiazide, and he demanded a transfer. He reported a 27-kg (60-lb) weight loss during the month before transfer.

The physical examination showed a well-developed well-nourished man who appeared to be in mild distress. The vital signs showed a blood pressure of 130/80 mm of mercury, pulse rate 96 and regular, respirations 12 per minute and temperature 36.9°C (98.4°F). There was a violaceous, confluent, painful, edematous rash on the fingers and toes with periungual infarcts and pustules. Palpable purpura was noted on both lower extremities. The neck was supple without thyromegaly and there was no adenopathy. The lungs were clear to percussion and auscultation. Examination of the heart elicited no murmur, rub or gallop. The abdomen was soft and nontender and had normal bowel sounds. The liver was 10 cm in span in the midclavicular line but the left lobe was enlarged. The spleen was easily palpable 4 cm below the left costal margin. The testicles were normal in size and consistency and without masses. Rectal examination showed no abnormalities and a guaiac test of a stool specimen was negative. There were tenderness and swelling of

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ABBREVIATIONS USED IN TEXT

AILD = angioimmunoblastic lymphadenopathy with dysproteinemia
ALL = acute lymphoblastic leukemia
HES = hypereosinophilic syndrome

several of the proximal and distal interphalangeal joints. There were no abnormal findings on neurologic examination.

A summary of the hematologic values during the six months before admission is given in Table 1. Of particular note is a progressive rise in the absolute eosinophil count, beginning about two months before admission and reaching a peak of 16,700 eosinophils per cu mm at the time of admission. Additional laboratory evaluation at the time of admission disclosed the following values: platelet count, 214,000 per cu mm; reticulocyte count, 0.8 percent; mean corpuscular volume, 111 cu μm; erythrocyte sedimentation rate, 15 mm per hr; prothrombin time, 10 seconds, and partial thromboplastin time, 33 seconds. Tests for antinuclear antibody, rheumatoid arthritis factor, VDRL and cryoglobulins were all negative. Thyroid function tests and a serum cortisol level were within normal limits. Values for blood glucose, serum creatinine and blood urea nitrogen were 143, 1.7 and 19 mg per dl, respectively. Serum electrolyte studies showed the following values: sodium 142, potassium 4.5, chloride 104 and carbon dioxide 23 mEq per liter. Total serum protein level was 6.8 grams per dl, albumin 4.6 grams per dl and calcium 9.9 mg per dl. Total serum bilirubin level was 0.6 mg per dl, the serum aspartate aminotransferase (AST, formerly SGOT) 40 units per ml, the lactate dehydrogenase (LDH) 289 units and the alkaline phosphatase 77 units per dl (normal, 35 to 105). Serum protein electrophoresis and quantitative immunoglobulin evaluations were within normal limits, as was a urine protein electrophoresis. Serologic tests for hepatitis B surface and core antigens and for hepatitis B core antibody were negative. Serum aldolase was 5.7 IU (normal, 1 to 6). Analysis of urine gave findings within normal limits, with no cells or casts noted in the urinary sediment. Results of pulmonary function tests were within normal limits. A roentgenogram of the chest and an electrocardiogram showed no abnormalities. A liver-spleen scan showed hepatosplenomegaly but no parenchymal defects.

The patient initially refused many procedures. However, a skin biopsy study showed ulceration and necrosis of the epidermis with infiltration of neutrophils. Small vessels of the upper and mid dermis showed deposits of a homogeneous eosinophilic material in the vascular lumens. There was no cellular infiltrate around these vessels. Additionally, there was a lobular proliferation of small blood vessels in the mid and lower dermis. No parasites were noted and there was no infiltration with eosinophils. Immunofluorescent stain showed fibrin but no immunoglobulin or complement.

On the third hospital day a diagnostic procedure was carried out.

Discussion

JOHN H. FITCHEN, MD:* There are several ways to approach this case. For example, one might approach it from the viewpoint of the differential diagnosis of vasculitis and, judging from the workup that was done, this was the approach taken by the ward team. Alternatively, one might consider this case from the standpoint of the differential diagnosis of eosinophilia, an option that I will exercise because of my interest in blood cells.

Background

Eos was the Greek goddess of dawn, the mother of Memnon. Her name, transposed by way of the name given to a brominated dye, eosin, now adorns the cell we call eosinophil. Although

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TABLE 1.—*Summary of Hematologic Values for the Six Months Before Admission*

	Date				
	4/10/80	*8/5/80*	*8/25/80*	*10/1/80*	*10/9/80 (Admission)*
Hematocrit (%)	..	38	33	..	38
Leukocyte count (per cu mm)	27,300	11,000	5,300	7,100	22,400
Segmented/band forms (%)	82/0	80/8	29/10	10/10	9/8
Lymphocytes/eosinophils (%)	10/0	8/4	35/25	62/16	7/75
Absolute eosinophils (per cu mm)	0	440	1,325	1,136	16,700

this cell was first described by Ehrlich more than 100 years ago, Beeson and Bass,[1] in their comprehensive monograph on the eosinophil, have said that "the complete ignorance of the function of the cell is one of the most humiliating and disgraceful gaps in all of medical knowledge." Nonetheless, this seems an appropriate forum in which to review what is known about this perplexing cell.

The eosinophil is a bilobed cell measuring 12 to 17 μm in diameter and containing densely packed eosinophilic granules. The average number of lobes per cell has been estimated at 2.06, but hypersegmentation is often seen in conjunction with eosinophilia. Receptors for the third component of complement and for the Fc portion of immunoglobulin molecules are present on the surface. The granules contain peroxidase, arylsulfatase, phospholipase, acid phosphatase, kinin and prostaglandin E.[1]

Most of our knowledge of the kinetics of the eosinophil is derived from studies in rats. In this animal model, the average marrow transit time is 5½ days. Eosinophils exist in the circulation in both marginated and circulating pools, and the half-life averages between three and eight hours. In the tissues, eosinophils tend to localize in areas exposed to the external environment (skin, mucosa, bronchi, gastrointestinal tract, lactating mammary glands, vagina and uterus). In fact the vast majority of eosinophils reside in the tissues, with the blood to tissue ratio being approximately 1:400.[1]

The exact functional role of the eosinophil remains an enigma. Based on circumstantial evidence, two putative functions have been proposed. First, eosinophils have been postulated to modulate inflammation. This suggestion is based on the finding that eosinophils are phagocytic for immune complexes and mast cell granules in vitro. In addition, arylsulfatase (one of the granule enzymes) inactivates the slow-reacting substance of anaphylaxis. A second proposed function is defense against parasitic infection. This proposal is based on the finding that eosinophils injure parasites in vitro and the fact that eosinophilia is more common with tissue invasion by parasites. However, eosinophils are rarely seen in contact with parasites in tissue sections.

There is some controversy regarding normal levels of eosinophils in the peripheral blood. In part this controversy is the result of analysis of absolute versus estimated eosinophil counts. Absolute counts are made by a hemacytometer on preparations stained with eosin dye, whereas estimated counts are obtained simply by multiplying the total leukocyte count by the percentage of eosinophils on a differential cell count. Estimated counts are probably accurate within 10 percent to 20 percent. In the literature, many articles simply list the percentage of eosinophils; this is clearly an unreliable guide. According to Beeson and Bass,[1] an eosinophil count above 350 per cu mm is abnormal; they found a mean of 120 per cu mm in healthy adults. In the bone marrow, eosinophils normally constitute up to 5 percent of the nucleated cells. Peripheral eosinophilia is always accompanied by an increase of eosinophils in the bone marrow.

The mechanism by which eosinophil production is increased remains to be fully elucidated. Before 1970 the major emphasis was on the study of eosinophil chemotactic factors. In 1970, however, Basten and Beeson[2] implicated T lymphocytes in the regulation of the production of eosinophils. These investigators studied *Trichinella* sp infection induced experimentally in rats. They first noted that plasma from rats with trichinosis did not produce eosinophilia when injected into normal rats. They therefore turned their attention to possible cellular mechanisms. They found that a reduction of T cells by neonatal thymectomy, by thoracic duct drainage or by antithymocyte globulin treatment resulted in decreased eosinophilic responses to trichinosis. Further, if normal thymic tissue was grafted into the thymectomized rats, a normal response to *Trichinella* sp infection was restored and when thoracic duct lymphocytes from infected animals were injected into normal rats, an eosinophilia was produced. Eosinophilia did not develop in congenitally athymic nude mice in response to parasitic infection. In later studies, Ruscetti, Cypess and Chervenick[3] noted that the addition of *Trichinella*-sensitized lymphocytes to bone marrow cultures favored the growth of eosinophilic colonies in vitro. Thus, there is a good deal of evidence implicating T lymphocytes in the regulation of eosinophil production.

Differential Diagnosis of Eosinophilia

With this background about the eosinophil in mind, let us now turn our attention to the case under discussion. The salient features of this case are a "vasculitic" rash, arthritis, weight loss, hepatosplenomegaly and prominent eosinophilia (a finding that was absent initially but pronounced

TABLE 2.—*Diseases Commonly Associated With Eosinophilia*

Parasitic (metazoan) infections
Nonparasitic infections (especially streptococcal)
Atopic diseases
Drug allergies
Skin diseases (pemphigus and pemphigoid)
Pulmonary eosinophilias
Hypereosinophilic syndrome (HES)

by the time of admission). I will approach the case by considering the differential diagnosis of eosinophilia, a subject that is covered in fascinating detail in the excellent book by Beeson and Bass.[1]

Disorders commonly associated with eosinophilia are listed in Table 2. The parasitic infections that produce eosinophilia are usually metazoan (Nematoda, Trematoda, Cestoda), with eosinophilia generally occurring in association with tissue invasion by parasites.[4] The patient had no history of travel, at least if the officials at the state penitentiary were doing their job properly. I will therefore not cover the subject of eosinophilia and parasitic infection extensively, but a few specific exclusions are in order for types that occur in the continental United States and that may be associated with dramatic eosinophilia.[4]

Toxoplasmosis can cause hepatosplenomegaly and eosinophilia but also produces lymphadenopathy, which the patient did not have. Prominent eosinophilia is common in ascariasis but hepatosplenomegaly is not seen. Patients with strongyloidiasis may have eosinophilia and hepatomegaly but the skin eruption that appears after penetration by the parasites is transient. Abdominal pain and diarrhea are also prominent features of strongyloidiasis and the patient had neither of these. Pronounced eosinophilia is common in trichinosis but hepatosplenomegaly is not seen. In addition, the patient did not complain of muscle pain or tenderness and the serum aldolase level was normal. *Toxocara* sp (visceral larva migrans) is associated with considerable eosinophilia and splenomegaly as well as rash and asthma. Fever and tender hepatomegaly are also prominent, however, and hyperglobulinemia is usually seen. Therefore, for the reasons stated, I do not believe this patient had a parasitic infection.

Nonparasitic infections (especially streptococcal infections) may be associated with eosinophilia. Scarlet fever is the best documented of these syndromes. In scarlet fever, the eosinophil count is maximal by the second or third week of infection and then falls dramatically, a pattern that differs from that seen in the patient. Tuberculosis deserves consideration because it could explain many of the findings in this patient and may be associated with an increase in eosinophils. However, tuberculosis is unlikely because the patient was afebrile and had a normal chest roentgenogram. In addition, pronounced eosinophilia is rare in tuberculosis and a decrease in circulating eosinophils is usually seen during periods of clinical deterioration.

Atopic diseases such as asthma and allergic rhinitis are often accompanied by mild eosinophilia, but there is nothing in the patient's history to suggest these disorders. Eosinophilia is commonly seen with allergic reactions to drugs, including sulfa-containing preparations such as trimethoprim-sulfamethoxazole. Because the patient's illness began before exposure to drugs, this seems an unlikely explanation for his eosinophilia.

Skin disorders are always listed in textbooks in the differential diagnosis of eosinophilia but this association is probably overstated. In fact, eosinophilia is characteristic only in pemphigus and pemphigoid and the patient did not have a bullous eruption.

An increase in circulating eosinophils is a frequent accompaniment of a group of disorders referred to collectively as the pulmonary eosinophilias. Loeffler's syndrome is characterized by cough and fluffy pulmonary infiltrates and remits spontaneously. Pulmonary infiltrates with eosinophilia (PIE syndrome) constitute a syndrome that is more severe than Loeffler's syndrome and is characterized by persistent symptoms and pulmonary infiltrates. Tropical pulmonary eosinophilia occurs in the tropics, is caused by microfilaria and is associated with very high IgE levels. Neither the patient's history nor the findings on chest roentgenogram support the diagnosis of any of the pulmonary eosinophilias.

A spectrum of diseases associated with eosinophilia, ranging from the relatively mild pulmonary eosinophilias to so-called eosinophilic leukemia, has been grouped under the designation hypereosinophilic syndrome (HES). Chusid and colleagues[5] defined HES as consisting of eosinophilia of more than 1,500 eosinophils per cu mm persisting for at least six months, evidence of organ infiltration by eosinophils and no other demonstrable cause of eosinophilia. The organs most frequently involved are the heart (95 percent),

TABLE 3.—*Diseases Occasionally Associated With Eosinophilia*

Vasculitides
Polyarteritis nodosa
Granulomatous vasculitis (Wegener's)
Hypersensitivity vasculitis
Rheumatoid arthritis
Inflammatory bowel disease
Pancreatitis
Neoplastic disorders

TABLE 4.—*Eosinophilia in Neoplastic Disorders*

Carcinomas
Lung
Colon
Pancreas (acinar cell)
Plasma cell dyscrasias
Lymphomas
Hodgkin's
Non-Hodgkin's
Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)
Acute lymphoblastic leukemia

the liver and spleen (80 percent), the lungs (40 percent) and the central nervous system (40 percent). In addition, 40 percent of patients have constitutional symptoms such as fever and weight loss. Although our patient had many features that were suggestive of HES, I do not believe he suffered from this syndrome in that he had reported eosinophilia for only two months; he had no historical, physical, radiographic or electrocardiographic evidence of cardiac dysfunction; he did not have persistent pulmonary complaints, and HES is a diagnosis of exclusion and no single diagnostic procedure could rule out all other possible causes of eosinophilia. One could argue that if the bone marrow showed a pronounced increase in eosinophils, prominent immaturity of the eosinophilic series and a distinctive karyotypic abnormality (for example, the Philadelphia chromosome), the diagnosis of eosinophilic leukemia should be entertained. However, eosinophilia occurred relatively late in this patient's course, suggesting that it was a reaction to an underlying pathologic process and not the primary event.

Diseases that are occasionally associated with eosinophilia are listed in Table 3. Eosinophilia is relatively infrequent in the vasculitides and is seldom pronounced. In polyarteritis nodosa, the number of circulating eosinophils is not increased unless there is pulmonary involvement with associated asthmatic symptoms. The patient had no findings to suggest granulomatous vasculitis such as Wegener's granulomatosis. Hypersensitivity vasculitis may also be associated with eosinophilia. Two specific causes of hypersensitivity vasculitis were ruled out by the ward team; namely, essential mixed cryoglobulinemia and the vasculitis that is associated with hepatitis B antigenemia. As indicated, the patient did have an atypical form of vasculitis, but this probably was a response to an underlying disorder (as was the eosinophilia) and not the cause of the eosinophilia per se. Eosinophilia is seen in rheumatoid arthritis only in seropositive patients whose disease is long-standing, severe and accompanied by pleuropericardial involvement.

Eosinophilia is occasionally seen in inflammatory bowel disease but, when present, is only mild. Severe and recurring pancreatitis may be accompanied by an increase in circulating eosinophils. Patients with this condition may have associated subcutaneous and periarticular lesions and polyarthritis. However, our patient had no symptoms to suggest the diagnosis of pancreatitis or inflammatory bowel disease.

Addison's disease is often listed as a cause of eosinophilia but this is probably a misconception because adrenocorticotropic hormone (ACTH) fails to lower the eosinophil count in patients with Addison's disease and recent studies have shown normal numbers of eosinophils in patients with this disorder. Before 1950 sarcoidosis was frequently mentioned as a cause of eosinophilia but this association has not been noted in the more recent literature.

Finally, eosinophilia has been occasionally noted in association with a variety of neoplastic disorders (Table 4). In a study from the Mayo Clinic of 418 patients with more than 20 percent eosinophils, malignant disorders were the underlying cause of eosinophilia in a quarter of the patients and lymphoreticular malignant disorders were the most common among these.[6]

Eosinophilia is occasionally seen with various types of carcinoma including carcinoma of the lung, colon and pancreas. Carcinoma of the lung seems an unlikely explanation for the patient's eosinophilia in view of his normal chest roentgenogram. Carcinoma of the colon, if metastatic, could produce hepatomegaly, but the patient had no gastrointestinal symptoms and it would be unusual for a colon cancer to produce splenomegaly. Acinar cell carcinoma of the pancreas has been reported in association with a syndrome characterized by eosinophilia, polyarthritis, tender skin nodules and panniculitis. Ten patients with this

syndrome have been reported in the the literature; all ten were men aged 50 to 70 years and skin biopsy specimens in these patients showed necrosis of the subcutaneous fat.[7]

Plasma cell dyscrasias, including multiple myeloma and Waldenström's macroglobulinemia, have occasionally been associated with eosinophilia. These disorders were ruled out in the patient on the basis of a normal serum protein electrophoresis and the absence of free light chains in the urine.

Eosinophilia has been reported in association with a variety of lymphoreticular malignant conditions, including Hodgkin's disease, non-Hodgkin's lymphoma and angioimmunoblastic lymphadenopathy with dysproteinemia (AILD). AILD was ruled out by the lack of adenopathy and the normal serum protein electrophoresis. Non-Hodgkin's lymphoma has been associated with both eosinophilia and vasculitis and may present as extranodal disease without adenopathy. However, non-Hodgkin's lymphoma is generally a disease of older persons and therefore seems unlikely in this young man. In contrast, Hodgkin's disease is relatively common in young people (especially young women). It has been associated with pronounced eosinophilia, can produce vasculitis,[8] and certainly would explain hepatosplenomegaly. However, dissemination of Hodgkin's disease to the liver, spleen and bone marrow without peripheral adenopathy would be distinctly unusual except in the lymphocyte-depleted histologic subgroup. Lymphocyte-depleted Hodgkin's disease most often occurs in older patients and is accompanied by fever, peripheral blood cytopenias including lymphopenia, and an elevated serum alkaline phosphatase level. These patients are usually very ill at the time of presentation.

The association of eosinophilia with acute lymphoblastic leukemia (ALL) was first described in 1973 by Spitzer and Garson.[9] Since then a total of 15 cases has been reported in the English-language literature.[9-16] The salient clinical and hematologic features of these cases are summarized in Table 5. Age of the reported patients ranged from 2 to 41 years and 13 of 15 were male. The development of eosinophilia preceded the diagnosis of ALL by one to nine months in five patients and predated relapse in three more. The absolute eosinophil count ranged from 330 to 110,000 per cu mm and was over 10,000 in eight patients. Lymphoblasts were not seen in the peripheral blood at presentation in seven cases

TABLE 5.—*Acute Lymphoblastic Leukemia and Eosinophilia: Laboratory and Clinical Features in 15 Cases*

Case No.	*Study*	*Age/Sex*	*Leukocyte Count (per cu mm)*	*Eosinophils (%)*	*Eosinophil Count (per cu mm)*	*Peripheral Blood Blasts (%)*	*Hemoglobin (grams/dl)*	*Platelet Count (per cu mm)*	*Eosinophilia Predisposition*	*Adenopathy*	*Splenomegaly*	*Comments**
1	Spitzer & Garson, 1973[9]	14/♀	132,000	83	110,000	3	13.0	86,000	Concurrent (predated 4 relapses)	−	+	CR with V,P
2	Spitzer & Garson, 1973[9]	16/♀	15,000	22	3,300	3	10.2	58,000	Concurrent	−	−	CR with Ara-C, 6-TG
3	Blatt et al, 1974[10]	9/♂	17,300	12	2,076	None	14.5	149,000	Yes (2 mos)	+	+	Loeffler's endocarditis, CR with P
4	Nelken et al, 1976[11]	12/♂	16,900	62	10,500	None	9.9	160,000	Yes (1 mo)	−	−	No response to V,P
5	Rizzo et al, 1976[12]	8/♂	13,700	35	4,800	None	10.6	30,000	Yes (2 mos)	−	+	CR with V,P,D
6	Pereira et al, 1977[13]	13/♂	84,600	83	70,200	None	8.1	231,000	Yes (9 mos)	NR†	NR	Fulminant course
7	Geltner et al, 1978[14]	17/♂	20,400	50	10,200	None	6.0	20,000	Yes (4 mos)	+	+	CR with V,P,D
8	Wimmer et al, 1978[15]	2/♂	129,000	71	91,600	2	10.1	85,000	Concurrent	−	−	CR with V,P, L-asp
9	Catovsky et al, 1980[16]	25/♂	16,900	53	9,000	None	12.0	30,000	Yes (3 mos)	−	−	CR with D, Ara-C
10	Catovsky et al, 1980[16]	17/♂	25,000	72	18,000	3	13.7	80,000	Concurrent	+	+	CR with TRAMPCOL
11	Catovsky et al, 1980[16]	41/♂	49,000	60	29,400	None	7.3	81,000	Concurrent	−	+	CR with COP
12	Catovsky et al, 1980[16]	4/♂	111,000	10	11,100	90	12.2	280,000	Concurrent	+	+	T-ALL: PR with V,P,D, L-asp
13	Catovsky et al, 1980[16]	23/♂	8,600	10	860	28	11.8	150,000	Concurrent (predated relapse)	+	+	T-ALL: CR with V,P,D, L-asp
14	Catovsky et al, 1980[16]	4/♂	10,600	11	1,170	19	8.3	34,000	Concurrent (predated 4 relapses)	+	+	CR with V,P
15	Catovsky et al, 1980[16]	6/♂	19,400	25	4,900	None	4.7	82,000	Concurrent	+	−	CR with V,P,D, L-asp

*Ara-C = cytarabine hydrochloride (arabinosylcytosine); C = cyclophosphamide; COP = cyclophosphamide, vincristine sulfate (Oncovin), prednisone; CR = complete remission; D = daunorubicin hydrochloride; L-asp = L-asparaginase; P = prednisone; PR = partial remission; T-ALL = T-cell acute lymphoblastic leukemia; 6-TG = 6-thioguanine; TRAMPCOL = 6-thioguanine, daunorubicin hydrochloride (Rubidomycin), arabinosylcytosine, methotrexate, prednisalone, cyclophosphamide, vincristine (Oncovin), L-asparaginase; V = vincristine.
†NR = not reported.

and were less than 5 percent in four more. Mild to moderate anemia and thrombocytopenia were frequently present, but a significant proportion of patients (8/15) had a normal hemoglobin level or platelet count. Adenopathy was absent or not reported in half the patients at presentation. Hepatosplenomegaly was noted in nine cases. A complete remission was achieved in most cases with various chemotherapeutic regimens. Thus, the typical patient with ALL and eosinophilia is a young male with pronounced eosinophilia, absent or low numbers of lymphoblasts in the peripheral blood, modest anemia or thrombocytopenia and hepatosplenomegaly with or without adenopathy, a constellation of findings remarkably similar to those noted in the patient under discussion. It should also be pointed out that vasculitis has been described in association with leukemia and lymphoma.[8] Recalling the experimental evidence implicating lymphocytes in the regulation of eosinophil production, it is interesting to speculate that the eosinophilia that occurs in patients with acute lymphoblastic leukemia is the result of excessive stimulation of eosinophilopoiesis by abnormal lymphocytes.

In summary, eosinophilia and vasculitis were probably both reactions to an underlying neoplastic disorder in this patient. The underlying disorder was most likely a lymphoproliferative malignancy. I assume that the procedure that was done was a bone marrow aspiration and biopsy and that the specimen showed a dramatic increase in eosinophils and the surprising finding of an infiltration with lymphoblasts. It is difficult to decide whether these lymphoblasts represented lymphoma or leukemia, but because the patient did not have lymphadenopathy and because he was a young man, I believe that he proved to have acute lymphoblastic leukemia.

Pathologic Findings

BARBARA HARTY-GOLDER, MD:* The bone marrow core biopsy specimen was hypercellular. A striking increase in eosinophils was present, with cells of all stages of maturation represented. Complete granulocyte maturation was seen and adequate numbers of megakaryocytes were evident. A diffuse infiltration of blast cells was present in the biopsy specimen (Figure 1). On aspirate smear, these blasts had scant cytoplasm, indistinct nucleoli and no Auer's rods or cytoplasmic granules. Peroxidase, alphanaphthol acetate esterase and Sudan black stains were negative. Periodic acid-Schiff (PAS) and acid phosphatase stains were positive, confirming the lymphoid origin of the blast cells. The pathologic diagnosis was acute lymphoblastic leukemia with reactive eosinophilia.

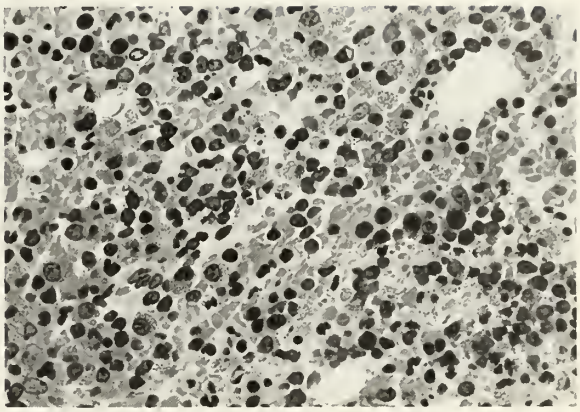

Figure 1.—Low power view of the bone marrow biopsy specimen showing a profound increase in eosinophils (cells with granular cytoplasm) and a diffuse infiltration with lymphoblasts. (Reduced from magnification ×680.)

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Important Advances in Clinical Medicine

Epitomes of Progress — Otolaryngology/ Head and Neck Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in otolaryngology/head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progess in otolaryngology/head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology/Head and Neck Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Snoring

MOST CASES OF EXCESSIVE SNORING are probably surgically correctable by resecting redundant segments of the soft palate and lateral pharyngeal walls. Though this has been a known and practiced operation in Japan for many years, the procedure—a palatopharyngoplasty—has only recently been "discovered" in the United States. It developed here as an alternative to tracheotomy for the treatment of patients with mild to moderate obstructive sleep apnea. Excessive snoring, which always accompanies this condition, was universally alleviated or reduced to levels that allow these patients' bed partners to sleep in the same room. Since the development of this procedure, patients with uncomplicated excessive social snoring have also been successfully cured.

The risks of the procedure are about the same as those of a tonsillectomy in an adult. Minor complications do occur in the form of occasional nasal regurgitation of liquids in some and slight dryness of the hypopharynx in others.

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Carotid Artery Management in a Radical Surgical Procedure of the Neck

THE CAROTID ARTERY poses a significant problem if it is involved with tumor or exposed during wound breakdown postoperatively. Efforts are being made to make management better organized and less threatening to patients. Carotid artery involvement by tumor is most often that of extensive metastatic squamous cell carcinoma of the head and neck, or large glomus tumors of the base of the skull and neck.

When carotid artery involvement is suspected preoperatively, angiography is indicated to identify tumor extent, arterial involvement and cerebral collateralization. During surgical extirpation of a neoplasm, the carotid artery is evaluated

directly and, if it appears necessary to remove the carotid en bloc, carotid artery backflow pressures are accomplished by directly catheterizing the carotid artery. If the backflow pressure is more than 50 mm of mercury, it is safe to proceed to remove the involved carotid artery. With these pressures patients will not sustain postoperative neurologic deficit. If pressures are less than 50 mm of mercury, a grafting procedure is done. Grafting may involve end-to-end anastomosis with a Gore-Tex (expanded polytetrafluoroethylene sutures) graft or vein graft. If an end-to-end anastomosis is not possible due to an inadequate distal carotid artery, a bypass graft involving an extracranial-to-intracranial graft may be necessary.

It may also be advisable to proceed with this type of carotid artery management in instances of massive neck wound breakdown following a radical head and neck operation. When the carotid artery is exposed and unprotected by dermal graft, early aggressive artery treatment may prevent catastrophic hemorrhage. We have found the early recognition of carotid artery involvement and its treatment a valuable addition to the care of patients with head and neck cancer.

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Carbon Dioxide Lasers in Managing Basal Skull Tumors

THE CARBON DIOXIDE LASER, of all lasers now available, seems best suited for surgical excision of neoplasms of the base of the skull. Our most extensive experience has been with treating acoustic neurilemoma tumors of the internal auditory canal and cerebellopontile angle. The carbon dioxide laser is strongly absorbed by water and thus is not color dependent, as is the argon laser. Rapid tumor reduction by the vaporization feature of the carbon dioxide laser is possible. It can easily vaporize nonvascular fibrous tumors as well as those that are highly vascular. Another clear advantage of the carbon dioxide laser is that it provides hemostasis at the time of tumor reduction, obviating the need for another instrument in the surgical field.

The carbon dioxide laser is a precise, gentle, light scalpel, producing no traction or compression of adjacent normal neural tissue. This laser is attached to an operating microscope and is controlled by a micromanipulator that allows precise placement of the helium neon-aiming beam. This aiming beam is important because the carbon dioxide laser is in the infrared spectrum and therefore invisible. A power density adjustment is useful in altering spot size and energy intensity, thus allowing a very small focal point for fine dissection or an increase in spot size for rapid tumor vaporization. Using the laser does not alter the mobility of the microscope as the laser head is separate, that is, connected to the microscope by an articulated arm.

We are impressed with the decreased operating time and postoperative morbidity with carbon dioxide laser use for basal skull tumors.

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Surgical Speech Rehabilitation After Total Laryngectomy

PROGRESS CONTINUES in surgical voice restoration after laryngectomy. The successful results of the tracheoesophageal puncture technique devised by Blom and Singer have been continued by others through multiinstitutional collaborative studies. The technique fulfills most of the criteria for surgical speech rehabilitation: it is simple; it may be accomplished secondarily to a surgical procedure (though recent investigators are reporting "primary" use of the technique, with patients leaving the hospital after a laryngectomy with full speech); it does not interfere with the original therapy (surgical or irradiation), and it is relatively free of complications. In addition, it is relatively successful with regard to the twin problems that plague procedures of this sort—stenosis and aspiration. It is far superior to any of the other "neoglottic" or glottic reconstructive procedures recently described.

On the negative side, though the procedure is simple and can be accomplished under local anesthesia, postoperative care is mandatory, but is much simpler than teaching esophageal speech.

There are a number of problems to overcome, such as prosthesis dislodgement, poor patient motivation and gastric distension. Close cooperation between the otolaryngologist and speech pathologist is mandatory.

With additional refinements, this is the best procedure for surgical vocal rehabilitation following laryngectomy available today. More recent efforts center on the development of an additional valve that will allow stomal closure (and speech) without the necessity of occluding the stoma with the finger or alternative valving mechanisms.

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New Treatment for Fractures of Edentulous Mandibles

FRACTURES OF EDENTULOUS MANDIBLES are a challenging problem. The nonunion rate has been reported at 20 percent. Most of the techniques require claborate external or intraoral fixation appliances or splints to adequately reduce and immobilize the fracture fragments. One technique, "dynamic and eccentric dynamic compression plating," has been reported by Levine and Goode at Stanford University Medical Center. This technique has been used to treat 20 fractures of edentulous, or nearly edentulous, mandibles with a 94 percent bony healing rate. Developed by Speissl and co-workers in Switzerland, it involves open reduction and application of an internal four-screw stainless-steel fixation plate that both fixates the fracture and applies constant compression to the fracture line, which has been shown in experimental animals to stimulate bony healing. This technique also provides normal mobility of the mandible during the healing period, allowing resumption of a relatively normal diet and daily activities.

The application of this technique not only holds promise for the treatment of fractures of the edentulous mandible, but also may prove useful for the treatment of fractures of mandibles with full dentition and in stabilizing bone graft fragments in the replacement and reconstruction of mandibles for traumatic and oncologic deformities.

PAUL A. LEVINE, MD

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Surgical Procedure for Progressive or Fluctuant Sensorineural Hearing Loss in Children

WHAT SHOULD BE our approach to children with a fluctuating sensory hearing level, a progressive loss of hearing, or both? Endolymphatic sac (ELS) operations have sometimes been suggested for patients with this problem, but it is only recently that a series of children has been shown to benefit from this type of procedure. Before recommending this type of intervention in this delicate and susceptible population, one must have a perspective of the procedure itself and a balanced approach to the parents and these unusual and perplexing patients.

ELS operations until recently have been shown to be of benefit only to adults with Ménière's disease (a rarity in children); the physiologic changes occurring as a result are unknown or sketchy at best. In children particularly an attempt at absolute diagnosis is essential before the designation "cochlear hydrops," which after all is a pathologic and only marginally clinical diagnosis.

A detailed maternal history (including pregnancy, delivery and the perinatal period), with a patient history seeking familial or pedigree problems, is mandatory. A story of vertigo should be sought but is very rarely a complaint in children. A perilymphatic leak from either window must be suspected, sometimes with little vestibular disturbance, and an objective fistula test with impedance bridge and electronystagmographic (ENG) leads is a minimum vestibular assessment. Late walkers or clumsy children should have a more formal test if old enough.

The examination should include neurologic, motor development, speech and language assessments. Audiometry examination with a check against recruitment is basic. An auditory brain stem response (ABR) or electrocochleographic pattern with high spikes or multipeaked waves has been described in association with the Mondini

anomaly (12/280 children with sensorincural hearing loss were found to have an anomaly and all had this pattern).

Serologic testing for lues, biochemistry studies for thyroid or renal dysfunction and serial viral titer determinations in mother and child may be required.

A polytomographic defect must be excluded on x-ray studies. It has been recognized that minor shortening of the cochlea may be a feature of the Mondini anomaly. The presence of such an anomaly does not of itself imply hearing deterioration and the other conditions should be satisfied before therapy is recommended.

A glycerol test should be done for both prognostic and diagnostic reasons. If findings are positive, a trial of salt restriction and oral administration of diuretics for three months is worth while. If findings are negative, this medical regimen (sometimes called conservative therapy) can still be used, though its continuation during a relentless hearing deterioration to the point that the ear is unaidable cannot be defended as "conservation."

At this point a surgical approach may be considered with the parents. The empiric nature of the procedure needs to be stressed together with the risks (5 percent profound hearing loss, 20 percent mild hearing loss). Stabilization of hearing, not restoration, is the aim, and this has been reported for the Mondini deformity only. This approach may be applicable to nonradiographically defective ears. Until further scientific evidence appears, however, we must exercise caution in our enthusiasm to help these unfortunate children.

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Cineradiography in the Evaluation of Obstructive Sleep Apnea

THE SYNDROME of obstructive sleep apnea is becoming more widely recognized by pediatricians, internists and otolaryngologists. In a recent issue of this journal, Rowe in his epitome "Obstructive Sleep Apnea" (1980 Oct; 133:324-325) gave a brief synopsis of this syndrome.

The use of cineradiography during normal sleep, that is, not induced by a sedative, is now an essential tool in the evaluation of obstructive sleep apnea syndrome. A patient is allowed to fall into a natural sleep in the radiology suite. During periods of both obstructed and nonobstructed respirations, the nasopharyngeal, oropharyngeal and hypopharyngeal structures can be functionally evaluated. This method allows a clinician to noninvasively determine whether there is obstruction due to poor support of the tongue musculature, a mass lesion or failure to maintain a supraglottic airway due to collapse of the lateral pharyngeal walls or the supraglottic laryngeal structures.

Use of this technique can assist head and neck surgeons and pediatric and medical colleagues to obtain a more accurate assessment of the anatomic cause of obstructive sleep apnea and, thus, allow more specific, definitive therapeutic intervention.

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The Treatment of Rhinitis With Topically Administered Steroids

THE TREATMENT OF vasomotor and allergic rhinitis is often quite difficult. Antihistamine and decongestant preparations given orally frequently produce the unwanted side effects of thickened secretions and central nervous system sedation or stimulation. Topically administered decongestants can produce rebound nasal obstruction, and dexamethasone aerosol has been shown to suppress adrenal activity. New flexibility is now available in the treatment of rhinitis since the Food and Drug Administration has recently approved the use of two new intranasal steroid sprays.

Beclomethasone dipropionate and flunisolide are both synthetic steroids that in multiple clinical studies have been more effective than a placebo spray in relieving the symptoms of vasomotor and allergic rhinitis. These effects are localized, and several studies cite examples of considerable relief of nasal symptoms with no effect on associated complaints of itching, burning eyes and excessive tearing. No adrenal suppression has been shown

with use as prescribed; however, suppression is possible with overuse of either preparation. *Candida* infection has not been a problem. Common side effects with both preparations include frequent nasal irritation and dryness that usually do not necessitate discontinuing treatment. Most reports show a decrease in the incidence of epistaxis with spray use, but there have been a few instances of mild epistaxis that have probably been related to use of the sprays. In two studies comparing the use of beclomethasone dipropionate with flunisolide, no significant difference was noted in their effectiveness or in the incidence of side effects. Patients and physicians favored the drugs equally.

Both sprays are contraindicated in the presence of an active nasal infection. Effectiveness is usually seen within the first few days to two weeks of use, and topical or oral administration of decongestants may be needed until effectiveness is shown.

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Digital Subtraction Videoangiography

DIGITAL SUBTRACTION VIDEOANGIOGRAPHY (DSVA) is a recent angiographic development in which a low level (2 percent to 4 percent) of contrast material is detected with a videofluoroscopic apparatus operating at one frame per second. The image is then converted to digital form that is in turn computer processed immediately by electronic subtraction and a number of electronic enhancement techniques. This technology was designed as a noninvasive method of detecting arteriosclerotic disease in high risk or low yield situations to obviate some of the disadvantages of conventional catheter angiography. It has been applied to the study of a wide range of vascular occlusive diseases, both diagnostically and to assess patency following vascular reconstructions.

DSVA is a study that is safe, economical, reliable and can be done on an outpatient basis with intravenous administration of contrast material. Selected catheter arteriography may also be carried out with this technology, with the advantages of reduced volumes of contrast medium and the availability of immediate subtraction views. Disadvantages of the study include deterioration of the quality of the study by patient motion and simultaneous visualization of all vessels with intravenous administration of the contrast medium.

Experience with this procedure in the past year has shown its usefulness in evaluating pulsatile tinnitus due to arteriovenous malformations, as well as in evaluating anomalous venous return and multiple myeloma of the temporal bone. Glomus tumors and other vascular tumors of the base of the skull have been evaluated and treatment response monitored. A vascular injury from a gunshot wound was also satisfactorily evaluated without conventional angiography. Vertebrobasilar artery patency and jugular venous patency have also been assessed.

Further experience is needed to more exactly define the role of this procedure. The greatest benefits appear to be a low risk method of screening vascular symptoms and lesions of the head and neck and a method for determining the presence of residual diseases and responses to treatment.

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Recent Advances in the Treatment of Serous Otitis Media

IN AN AWARD-WINNING random study, Gebhardt reported the efficacy of tympanostomy and ventilating tubes for the treatment of recurrent otitis media. In a prospective study tympanostomy with tube placement was shown to significantly decrease the number of episodes of acute otitis media and to be an effective method of prophylaxis for an otitis-prone child, when compared with conventional antibiotic therapy.

The long-term effects of untreated middle ear effusion on learning ability were studied during the past year. Auditory processing abilities in children with persistent middle ear effusions have been a matter of concern since animal studies showed permanent anatomic deficiencies in the

central auditory pathways were associated with early auditory deprivation, suggesting that lack of auditory input at a critical stage would result in failure of development. The question of whether partial hearing deprivation (as might occur with serous otitis media, either intermittently or continuously) can result in subsequent language and hearing abnormalities was studied among siblings who differed only in their history of ear effusions (controlling, therefore, for social input, environment and so forth). The group that had effusions, while developing no significant deficit in overall IQ, did much poorer on auditory test scores and verbal IQ scores than matched siblings without effusions. Interestingly, the group with effusions had (apparently) compensatorily higher visual test scores. These data suggest that children with untreated middle ear effusions will do better in educational programs that use teaching methods based on visual sequential memory skills and that these may be helpful in enhancing rehabilitative efforts.

Thus, recent studies have verified what has long been felt to be true, that tympanostomy tubes are effective in the treatment of serous otitis media and that failure to vigorously treat this "minor" problem will result in communicative handicaps that may be life-long.

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EDITORIALS

The Payors' Revolt

One of the things that was probably predictable, but seldom predicted, is that, as third parties in both the public and private sectors begin to pay for more and more of health care at greater and greater cost, sooner or later they would rebel at the cost, and now there has been a definite payors' revolt in California. The outcome remains to be seen as does the extent to which the effects may be felt throughout the West and elsewhere. Two bills in California (AB 799 and AB 3480) were fashioned largely behind closed doors without public comment, passed by the California Legislature and on June 30, 1982, signed into law by California's governor. It might be added that this was done almost gleefully, and over the opposition of the California Medical Association and others.

It seems clear enough that what happened is a result of mounting frustration with the rising cost of health care with no end in sight, not only in the government but in industry, labor and other third parties in the private sector who must pay for health care, and some might add with their perception of an unwillingness or inability on the part of the medical profession to deal effectively with these rising costs. Put very simply, these new laws allow government and private insurers to contract with hospitals and physicians or groups of physicians to become preferred providers of health care at alternative and presumably lower negotiated rates, and also in many instances would significantly curtail or eliminate freedom of choice for a patient seeking health care. The impact of this upon the quality of care for those who would then have little or no freedom of choice is not known, but the earlier experience in California with prepaid health plans for persons medically indigent was not favorable.

The frustration that led to these hasty and some would say ill-considered actions is real. It remains to be seen whether they will make matters (including the frustrations) better or worse. To the extent access to each is reduced the overall quality of care is certain to be adversely affected. The experience to date with hastily conceived legislation in health care has generally been that more problems are created than are solved without there being much if any improvement in either quality or cost of care. But of even more concern in this instance is that the legislation rides pretty much roughshod over the legitimate interest of those who are at the very heart of health care—that is, those who must render it and those who must receive it. This causes one to wonder whether health care is now to be arranged to satisfy the payors (who generally are not sick) or to meet the needs of patients who generally are sick and are the ones in need of the care. It would seem that fair and equitable solutions have yet to be found for these pressing, present and growing problems in health care and the genuine frustrations they engender.

No doubt there will be attempts to modify this legislation in behalf of good care for patients, but the fact remains—something significant has happened in the West.

—MSMW

Mast Cells and Homeostasis: Another View

It is a great temptation to consider mast cells solely in the context of disease. The numerous arguments for this orientation reflect the lengthening list of preformed and newly generated mediators of immediate hypersensitivity, as viewed from the standpoint of their pathobiologic effects. Indeed, as Drs. Marquardt and Wasserman point out in their review, the untoward consequences of mast cell activation and degranulation are impressive: bronchospasm, increased vasopermeability, anticoagulation and tissue infiltration by leukocytes. It thus requires a major shift from the usual frame of reference to speculate as to whether mast cells, with their wide distribution among the organ systems, subserve any function in host defense and homeostasis for healthy organisms.

Hypothetically, mast cell granule-associated preformed mediators have the capacity for a number of "housekeeping" activities in their immediate milieu. Because mast cell-derived acid hydrolases and protease have the combined capacity for metabolism of collagen and proteoglycan ground substance, they have the potential for directly

increasing removal of cellular debris. Further, as an enhancer of vasopermeability, histamine may recruit molecular and cellular elements from the vascular compartment to the tissue interstitium such that clearance of damaged cellular material from the normal life and death process of cell turnover is augmented. It is remarkable that the distribution of mast cells among organ systems is greatest for those with rapidly turning-over (epidermal or mucosal) cell populations and is notably absent only from the central nervous system, where cell turnover is the least. Additionally, rapidly replicating tumor cell populations may induce mast cell proliferation in their immediate environment via an activity recoverable from crude tumor angiogenesis factor preparations.[1]

Because mast cell membrane lipid turnover and degranulation occur as a localized event, the vasodilation and permeability-increasing effects of histamine, prostaglandin (PG) D_2 and slow-reacting substance leukotrienes generated in nonrespiratory tract tissues may be significant locally; whereas the mediator concentrations available to distant nonvascular smooth muscle and mucosa after dilution and metabolism in the circulation may normally be of little consequence for airway smooth muscle tone or nasal secretion. Likewise, although mast cell heparin release has only rarely been reported to be of systemic consequence for anticoagulation,[2] locally available heparin may be sufficient and necessary to prevent thrombogenesis when, under the influence of altered vasopermeability, procoagulant factors of plasma enter the collagen-rich tissue interstitium.

Consequent to having raised the question of normal monitoring functions for the tissue mast cell, a second critical issue concerns whether such putative functions may be IgE-initiated, as are the pathobiologic allergic responses. Another way of addressing this issue is to ask whether the total absence of IgE might be harmful rather than beneficial to humans. This is not simply answerable from health assessment of persons lacking measurable circulating IgE, because some of those subjects have positive allergen-reactive skin tests, which may be mediated by cell-bound IgE, and reflect the relatively long half-life of this IgE population as compared with that of the circulating immunoglobulin.[3] However, the answer, when obtained, will have direct influence on future directions for immunotherapy of atopic persons, in regard to whether down-regulation of allergen-specific IgE synthesis is theoretically preferable to global suppression of total IgE production. Further, because mononuclear cells and macrophages are also known to bind IgE by specific receptors, albeit of relatively low affinity,[4] the issue of IgE effects on homeostasis and host defense against certain parasites[5] may supersede limited considerations of mast cells and basophils.

The signal function by which dimerization of adjacent IgE molecules and, secondarily, of their receptors, regulates both secretion of preformed mediators and the de novo synthesis of both PGD_2 and the slow-reacting substance leukotrienes[6-8] has developed in association with certain membrane-associated enzymes[9,10] so as to allow fine gradations of dose-related mediator release. That the signal-response ratio is highly regulated suggests the potential for modest IgE-dependent stimuli to evoke mediator-dependent events that are protective against the extension of moderate to minor tissue insults. More severe tissue insults could then evoke "disease" either by overwhelming homeostatic controls or, as in allergy, provoke a high level of mediator release, which itself elicits the major pathobiology. For a given mast cell population the level of antigen-induced mediator release depends not only on the concentrations of offending antigen, but also on the number of pairs of adjacent IgE receptors occupied by IgE recognizing that antigen; however, reduction of specific IgE in an atopic person should reduce antigen-dependent mediator release below the level at which allergic symptoms are appreciable, but possibly not to the extent of completely eliminating mediator release. Further, IgE-dependent mast cell and basophil mediator secretion can be effected via dimerizing adjacent IgE molecules by linking the oligosaccharide residues of their Fc regions, as has been shown for the plant lectin concanavalin A.[11] Thus, the possibility exists for linkage factors to act on constant, rather than variable, IgE domains and so to effect IgE-mediated mast cell degranulation in the absence of specific antigen or at low levels of antigen-specific reaginic antibody. As indicated by Marquardt and Wasserman an additional number of cell secretagogues effect degranulation independent of IgE or of its receptor.

It would be simplistic to consider the bioavailability of preformed granule-associated activities and of those newly generated as being in a fixed ratio or that these compounds need act independently. From our own unpublished studies in IgE-mediated models, arachidonic acid metabolism appears to be more sensitive than granule secretion

to low levels of IgE-dependent activation. Even the process of mast cell granule secretion appears to be a divisible event in terms of the bioavailability of different granule-associated mediators, some of which are more readily diffusible from the granule matrix and others less so. It would be of intrinsic benefit to an organism if local mast cell activation were regulated not only quantitatively but also qualitatively with respect to the ratio of bioavailable mediators under various circumstances and reflecting the specific requirements of homeostatic regulation from time to time.

Marquardt and Wasserman have written, in this issue of the journal, an excellent and encyclopedic review of mast cell mediators and their potential relevance to disease. That the present state of the art indeed favors this view of the mast cell, to the exclusion of consideration of mast cell function in health, is consistent with the relative ease of developing laboratory models for pathobiologic responses and the difficulty of studying the less remarkable variations of the microenvironment postulated for maintenance of homeostasis. Given that homeostasis is the basis for the return to normal function from the minor variations of daily environmental insults and disease only a breakdown in homeostasis, some new approaches are needed to appreciate the function of mast cells in a broadly distributed regulatory system of the healthy organism.

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Paranoia and Nuclear Armaments

THE RECENT PROTESTS against nuclear armaments obviously struck a responsive chord throughout the Western world. No one who knows anything about it, and who is in his right mind, can really want nuclear warfare. Somehow it must be avoided. Yet we see the two nuclear megapowers standing off against one another, with yet others building up their nuclear power in the wings. The present arms race suggests that fear on both sides of the Iron Curtain is approaching the point of paranoia. It is important to note that the public protests on this side of the Iron Curtain have not been matched by similar protests on the other side. In fact it was reported that one small attempt at public protest on the other side was quickly quelled by the police. One of the nuclear megapowers permits public protest while the other does not. There is a standoff in political belief as well as in nuclear armaments. But paranoia can become a very dangerous form of insanity and it can affect the leaders as well as the masses of people. Somehow sanity and reason must prevail in both camps. The insane alternative is literally unthinkable.

The barriers to reasoned communication back and forth across the Iron Curtain are formidable. If there is to be reasoned communication some common ground for it must be sought. Could there be any common ground other than interminable talks about arms reduction, a process which by itself tends to feed, and to feed upon, paranoia? To this simple health professional it seems that both nuclear megapowers are beginning to have problems pertaining to the health of their citizenry which could be relieved if the economic resources allocated to nuclear arms were redirected toward meeting more human needs. One megapower cannot even feed its populace, let alone provide the durable goods they have worked for so long, and the other is finding that it can no longer afford the health care for the aged and needy that its people have come to expect. Could it be that it is in the social and economic interests of both to agree to a fundamental change in their priorities? This seems possible, but not very likely to happen if the agenda of one continues to include conquering the world (while at the same time accusing the other of

being imperialist), and seems not even ready to think the unthinkable, whether this be a conquest of the world or the aftermath of nuclear war.

Meanwhile that little devil paranoia is hard at work trying to keep sanity at bay. If the little fellow can succeed in preventing the reasoned communication that is necessary, and eventually comes to dominate the minds and hearts of leaders and the populace of the two nuclear megapowers, then that little devil could just have won for itself whatever might be left of the world.

—MSMW

In Defense of the Bladder

BLADDER URINE IS customarily thought of as being sterile in the absence of infection. This concept is probably not entirely valid as small numbers of bacteria can be shown to enter readily into the bladder urine after gentle massage of the female urethra.[1] The bladder is probably intermittently challenged by bacteria migrating along the continuous mucosal surface of the urethra and bladder. How then does the urinary bladder defend itself from infection?

This question was addressed some years ago by a series of experiments carried out by Cox and Hinman.[2] They showed that a bacterial inoculum introduced into the bladder of healthy volunteers could be eliminated after several spontaneous voidings. In contrast, the same urine specimens could not be sterilized when voided into and emptied repeatedly from a glass tumbler. The bulk of the bacterial load was removed simply by repeated voiding. This may be termed as the *primary bladder defense mechanism*. O'Grady and Cattell[3] have shown that a high fluid intake combined with frequent voiding and a small residual volume can result in fall in bladder bacteriuria in infected patients from 10 million to 100 in only seven hours. How then are the remaining bacteria removed? Organisms caught in the thin film of urine could not be removed from the tumbler by repeated emptying in the Cox and Hinman study, but could be eliminated naturally by the normal human bladder.

The effect of the bladder mucosa on these small numbers of residual bacteria can be considered the *secondary bladder defense mechanism*. There are several independent explanations as to how the mucosa may prevent infection. Vivaldi, Kass and others[4-6] showed a killing effect by the bladder mucosa on organisms clinging to the surface fluid. An additional explanation is offered by Parsons and co-workers.[7] A glycosaminoglycan is secreted by the bladder mucosal cells onto their surface. This polymer greatly reduces the ability of the bacteria to adhere to the mucosa. More recently Örskov and associates[8] have reported that a bacteria-fixing slime found in abundant amounts in normal urine and tracheal secretions can trap *Escherichia coli* with type 1 fimbriae. The substance appears identical to Tamm-Horsfall protein. This glucoprotein contains mannose in its carbohydrate chain. The importance of this sugar on binding of bacteria to cell surfaces will be described later on.

The *tertiary bladder defense mechanism* may be characterized as the bacterial growth inhibitory characteristics of urine. Consider, for example, the fact that gonococci, though abundant in the urethra during acute infection, do not invade the bladder. McCutchan and colleagues[9] have shown that acid urine with high tonicity is bactericidal against these organisms. Anaerobes do not grow well in urine. This is in part due to the presence of dissolved oxygen. Many other fastidious bacteria are inhibited by urinary constituents.[10] Even the growth of Enterobacteriaceae, which commonly causes urinary tract infections, is inhibited by dietary-derived organic acids, low pH and high concentrations of urea.[11-12]

Given this extraordinary set of known defenses and probably others that will be described in the future, it is not surprising that a hostile environment must be overcome by invading microorganisms. Furthermore, low doses of antimicrobial agents can prevent surface attachment and inhibit growth of small numbers of bacteria that may intermittently enter the bladder. This could explain the efficacy of single-dose therapy in uncomplicated infections or low-dose prophylaxis described by Stamm in this issue.

One of the major difficulties in the field of urinary tract infections has been to distinguish between bacteria truly growing in bladder urine and those that simply colonize the urethra and adjacent structures. The quantitative bacterial count in voided urine has proved useful for most clinical situations. Unfortunately, it cannot be used to distinguish contamination from infection for more fastidious organisms. The Seattle group have, for example, presented data indicating that the urethral syndrome may be due to small numbers of enteric bacteria.[13] They use pyuria as a distinguish-

ing feature for these infections and those due to *Chlamydia*. In contrast, Maskell and her colleagues[14] working in Britain have proposed that fastidious organisms including *Corynebacterium* sp and lactobacilli are responsible for the syndrome. Both groups point as proof to the "gold standard" of finding bacteria in specimens obtained by suprapubic aspiration in symptomatic patients. Brumfitt and co-workers[15] examined this question and could not confirm Maskell's hypothesis, nor confirm or refute the work of Stamm and associates. For example, suprapubic aspirates obtained from 44 women with the "frequency and dysuria syndrome" revealed no cells or bacteria in the urine.

Even when microorganisms are recovered from suprapubic aspirates, how should their presence in the urine be interpreted? We already know that bacteria can intermittently enter and leave bladder urine. Thus when organisms are recovered, are they simply in transit or are they established invaders? Several studies have reported the presence of fastidious microorganisms in suprapubic aspirates from normal or pregnant women.[16,17] In one study by McDowall and associates,[16] for example, *Gardnerella vaginalis* and *Ureaplasma urealyticum* were commonly isolated by suprapubic aspiration. Similarly, McFadyen and Eykyn[17] reported the isolation of slowly growing, fastidious bacteria from urine obtained from the bladders of 15.9 percent of 1,000 pregnant women. We can conclude from these studies that the urinary tract is more constantly exposed to potentially invading organisms than previously believed.

Part of the reason for difficulty in distinguishing infection from contamination by commensals is the remarkably circumscribed, yet overlapping, microbial ecosystems in the perineal region. The anal area contains abundant enteric bacteria, including the well-known coliforms and even larger numbers of anaerobes. The vagina has an exceedingly complex, mostly anaerobic flora consisting of lactobacilli and at least 36 other species.[18] The relative abundance of these organisms is altered during the menstrual cycle, with age and by antimicrobial agents. The periurethral and urethral flora are also distinct, containing *Staphylococcus epidermidis,* lactobacilli, *Corynebacterium* and *Bacteroides* species. What then enables one organism to dominate the others, to establish continued growth in the bladder urine and to be in a position to invade the upper urinary tract?

Much of the work in recent years has emphasized the invasive properties of enteric bacteria, particularly *E coli,* which produce most urinary tract infections. The contributions by Stamey and his group[19] were well summarized some years ago in the predecessor of this journal. They offered convincing evidence that urinary tract infections are preceded by colonization of the urethra by the invading organisms. They also examined local factors such as the pH, glycogen and immunoglobulin content of vaginal secretions that might influence colonization. They proposed that the urethras of women prone to infection are more likely to be colonized by *E coli* than others. There is not, however, uniform agreement on this point[20,21] and the protective role of immunoglobulins in the vagina has been questioned.[22]

We are now witnessing a see-saw effect in the literature that on the one hand suggests that the vaginal, bladder and urethral cells of women with recurrent infection have more abundant receptors to enteric bacteria[23] and on the other hand studies that indicate that some bacterial strains are more "uropathic" because of fimbriae that can readily attach to these cells. Compounding the issue are the difficulties in quantitating cellular adhesion by bacteria and the relatively excellent growth properties of these organisms in urine. It is also unclear whether the same biologic properties that govern colonization of the bladder are related to invasive properties for the kidney. The growing field concerned with the ability of enteric bacteria to attach to mucosal cells and colonize the urinary tract is beginning to overlap with studies of attachment and invasion of the gut.

In brief, this new field emphasizes the role of pili or fimbriae, small hairlike projections from the body of the bacteria. Type 1 fimbriae contain receptors for mannose on the host cell surface. These receptors are present in a variety of cells including not only the bladder epithelium but the buccal mucosa and erythrocytes as well.[24] Mannose added to the medium can elute attached organisms and prevent bacterial colonization, hence the possible role of Tamm-Horsfall protein as a defense described above. There are other fimbriae that do not depend on mannose for binding to receptors. These allow the bacteria to attach in the presence of this sugar. Several groups of Swedish investigators[25,26] have emphasized the role of these fimbriae as being of special importance in characterizing pyelonephritogenic strains of *E coli.* The terminal sugars of the cellular receptors are located on membrane glycosphingolipids of the P

blood-group system that are present in urothelial cells as well. The key determinants are galactosyl-galactose residues. Because few people lack this system, that is, they are P-substance negative, it would be unlikely that absence of this binding site would differentiate the large group of women who are susceptible to recurrent infection. A clue to differences in susceptibility to pyelonephritis among children is suggested by the recent report of Lomberg and co-workers.[27] They found that erythrocytes of children with recurrent urinary tract infections were more commonly seen in the P1 blood group than otherwise healthy controls (27/28 with recurrent urinary tract infection versus 30/40 in controls, $P = <.02$). This subtle difference in the P blood group offers a possible explanation of susceptibility to infection. Because 75 percent of humans are P1 positive, most of us would be at risk of infection.

Urinary tract infections are deceptively simple events. They are commonly encountered in practice and so readily treated that sophisticated clinical investigators might wish to work in seemingly more challenging areas. It is amply clear from the excellent review by Stamm in this issue and from the points I have raised in this editorial that we are dealing with a very complex series of host-parasite relationships. The field has recently moved to the molecular level of cellular receptors. One wonders whether a fimbrial vaccine can be developed and a target population selected to exploit these new findings. Such a vaccine would have to compete with the remarkable efficacy and low cost of bedtime prophylaxis for those with frequently recurring infections. Even if host resistance could be enhanced, the question remains whether this could overcome gross hydrodynamic and structural defects in patients with infections complicated by foreign bodies or obstruction. One has only to look to the disparate efficacy of the pneumococcal vaccine in young South African miners where it was remarkably effective, as opposed to elderly Americans in whom efficacy appears to be marginal. Despite these reservations we can look forward to exciting developments in this field.

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The Enigma of the Eosinophil

THE EXCELLENT case conference in this issue by Bachhuber and colleagues concerning a young man with vasculitis and pronounced eosinophilia contains a discussion of what is known—and what is not known—about the function of the eosinophil. I have a special interest in this cell and have made a fairly extensive study of clinical and experimental literature concerning it. Dr. Fitchen

mentioned my frustration.[1] Readers are referred also to another discussion on this topic.[2]

Almost certainly this cell should not be looked on as a granulocyte with special staining properties. It differs greatly from the neutrophil in its behavior—for example, in acute infections or after administration of adrenal glucocorticoid hormone. Indeed, eosinophils usually behave as though they were part of the immune apparatus rather than of the phagocyte family.

Is the eosinophil a vestigial cell that now serves little or no purpose? That seems unlikely, in that eosinophils are present in all mammals in about the same numbers; furthermore, in experimental situations their behavior is remarkably predictable. Absence of eosinophils from human bone marrow has been observed very rarely and never in other mammals, to the best of my knowledge. We probably should assume that eosinophils serve some specific function or functions. But what can these be?

Two hypotheses are actively pursued, and the respective "colleges" of investigators appear to presume that one or another is going to give us a satisfying answer. One possibility is that they serve as antagonists to basophils, dampening the effects of the potent pharmacologic substances liberated when basophils (or mast cells) degranulate. A second possibility is based on evidence that eosinophils protect against metazoan infestations. Both points of view may be correct, but somehow they do not seem wholly satisfying. I think that with the information available at present we should keep an open mind about the matter.

One problem for those who try to carry out in vitro experiments with eosinophils is the difficulty in separating adequate quantities of them uncontaminated by other leukocytes. Most such work relies on cells taken from fluid exudates, or buffy coats, of patients with eosinophilia, or from inflammatory exudates of animals in which eosinophilia has been induced. It is virtually impossible to separate "pure" suspensions of eosinophils from such starting materials. Furthermore, the eosinophils obtained for study are likely to be "abnormal," having been activated by disease or an antigenic stimulus.

As Fitchen notes in his discussion, surveys of the clinical literature on eosinophilia do not provide good leads to their function. The striking thing is that an eosinophilic response (except in the case of metazoan parasitic invasion) occurs in only a few cases of, say, skin disease, allergy, drug sensitivity or neoplasm. Increased production in those instances may be an aberrant reaction, comparable to ectopic hormone production.

Perhaps we should give more thought to the possibility that this cell serves in some other manner than to protect us against external invaders. Perhaps instead its function is related to maintenance of homeostasis. Certain points can be cited to support such a notion. One is the diurnal variation in numbers of eosinophils in the circulation (higher in the early morning and lower in the late afternoon). Another is the finding that when careful quantitative counts are made in healthy people, substantial variations are found to be occurring from minute to minute, all within the normal range. Another point is the known effect of certain hormones (glucocorticoids, epinephrine and estrogens) on the number of circulating eosinophils.[1] With regard to the estrogens, there is impressive clinical information to show that men are more likely to exhibit eosinophilia in many disease states. This holds for the syndrome discussed by Fitchen and his Table 5 shows that 13 of 15 patients who had prominent eosinophilia as a manifestation of acute lymphocytic leukemia were male, as was his patient. When we turn our attention to the eosinopenic effect of epinephrine, it is interesting to note that the phenomenon can be prevented by administration of a β-blocker such as propranolol. Also, if propranolol is given alone it causes a rise in the number of circulating eosinophils.

Could the eosinophil serve as a carrier of hormones to their sites of action? Could it act as a buffer, or a slow-release mechanism, to counter the effects of excessive liberation of certain hormones? Possibly the solution to our enigma will emerge from work in the neurosciences or endocrinology.

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CASE REPORTS

Refer to: Avner DL, West HC, Rikkers LF: Bilious ascites simulating tuberculous peritonitis. West J Med 1982 Sep; 137:241-243

Bilious Ascites Simulating Tuberculous Peritonitis

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BECAUSE THE RELATIVE INCIDENCE of extrapulmonary tuberculosis appears to be increasing and it is often more difficult to diagnose than its pulmonary counterpart, physicians have been appropriately urged to maintain a high level of suspicion for its subtle forms of presentation.[1,2] It has been cautioned, however, that failure to provide histologic or bacteriologic confirmation of extrapulmonary tuberculosis may be erroneously inflating the case rate.[2] The following report describes a patient with asymptomatic bilious ascites who presented with clinical and laboratory features suggestive of extrapulmonary tuberculosis. This report emphasizes the need to confirm the diagnosis of extrapulmonary tuberculosis by other than skin testing and, additionally, represents the first case report of asymptomatic bilious ascites resulting from spontaneous perforation of the gallbladder wall.

Report of a Case

A 60-year-old man was admitted to the Salt Lake City Veterans Administration Medical Center on June 13, 1980, for evaluation of an increase in abdominal girth of five weeks' duration, associated with a 9-kg (20 lb) weight loss, night sweats and a temperature to 38.3°C (100.9°F). Diffuse lower abdominal pain was present for approximately five days and then disappeared. He had a moderately heavy alcohol intake in the past, but said that there had been no previous ascites, jaundice, hepatitis, gastrointestinal bleeding or cardiac or respiratory disease. The patient was admitted to a hospital elsewhere after two weeks of illness and the following pertinent information was obtained. The complete blood count and differential leukocyte count gave findings within normal limits. A serum alkaline phosphatase level was 328 units per liter (normal, less than 115); the results of other liver enzyme studies were normal. A diagnostic paracentesis showed a brown fluid, analysis of which produced the following: an erythrocyte count of 14,550 per cu mm, a leukocyte count of 100 per cu mm (74 percent polymorphonuclear cells and 26 percent lymphocytes) and an amylase level of 25 units per dl (the total protein level was not measured). Culture of the ascitic fluid was negative for aerobic organisms. Cytologic examination showed no tumor cells but atypical lymphocytes were present. Results of a barium enema study, upper gastrointestinal series, computerized tomography of the abdomen and selective angiography of the hepatic and splenic arteries were all normal. Despite oral administration of 2 grams of ampicillin a day, fever and ascites persisted and the patient was transferred to the Veterans Administration Medical Center.

On physical examination at admission the patient was noted to be obese but seemed in no acute distress. His blood pressure was 120/80 mm of mercury, pulse rate was 100 per minute, respirations were 15 and temperature was 37.2°C. Cardiac examination showed no abnormalities. Inspiratory rales were heard at both lung bases on auscultation of the chest. The abdomen was protuberant but nontender to palpation. Shifting dullness and a prominent fluid wave were detected. There were no masses, organomegaly, venous distention or bruits. Results of genital, rectal and stool examinations were normal.

Initial laboratory tests gave the following values: hematocrit, 35 percent; hemoglobin, 11.1 grams per dl; leukocyte count, 11,100 per cu mm, with a normal differential count; platelet count, 650,000 per cu mm; total protein, 6.7 grams per dl; serum albumin, 2.6 grams per dl; serum alkaline phosphatase, 227 units per liter (normal, less than 115); serum aspartate amino transferase, 26 units

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per liter, and total bilirubin, 0.7 mg per dl. X-ray studies of the chest showed old calcified granulomas and small bilateral pleural effusions. A diagnostic paracentesis yielded 60 ml of dark brown fluid with an erythrocyte count of 130,000 per cu mm; a leukocyte count was 600 per cu mm, of which 40 percent were segmented cells, 56 percent were lymphocytes and 4 percent were monocytes. The amylase level was 25 units per liter and the total protein level was 1.3 grams per dl. Gram stain, cultures for bacteria and cytologic examination of a specimen of the ascitic fluid were all negative. Cultures of urine and blood specimens were also negative.

Throughout the first hospital week he had a low grade fever (38.1°C). A tuberculin skin test (5 TU of Tween-stabilized purified protein derivative-tuberculin) produced 9 mm of induration. Peritoneoscopy showed small, yellowish white papular plaques (3 to 5 mm in diameter) and inflammatory lesions studding the entire peritoneal surface. Greenish yellow strands of adhesive exudate bridged the viscera with the anterior abdominal wall. The liver appeared normal in size and texture. Peritoneal biopsy specimens were obtained for culture and histologic examination. Analysis of ascitic fluid obtained during peritoneoscopy showed an erythrocyte count of 24,000 per cu mm and a leukocyte count of 2,700 per cu mm, with 22 percent polymorphonuclear cells, 66 percent lymphocytes, 2 percent monocytes, 1 percent eosinophils and 9 percent mesothelial cells. The peritoneal biopsy specimens showed only fibrosis and nonspecific inflammation. Findings of Ziehl-Neelsen and Gram stains were negative, as were routine cultures for bacteria and fungi.

Although peritoneal tuberculosis was still considered a possible diagnosis, it was decided to do an exploratory laparotomy to obtain more tissue and exclude other occult causes of illness. At laparotomy the abdomen contained 9,500 ml of brown ascitic fluid and the peritoneum was diffusely covered with nodular plaques and green exudates. For the sake of thoroughness the surgeon carefully palpated the abdominal cavity and to his surprise discovered three pigmented gallstones in the pelvis. The gallbladder, which was densely adherent to the duodenum and omentum, was carefully examined and found to contain three additional gallstones; a 1.0 by 1.0 cm perforation was then detected midway between the neck and fundus. The cystic duct was patent and bile appeared to flow freely from the gallbladder. The lateral wall of the right upper quadrant, the subhepatic space and the hepatoduodenal ligament were all stained with bile. Following normal findings on an operative cholangiogram, a cholecystectomy was carried out. The patient recovered uneventfully without recurrence of ascites.

Discussion

The clinical features of low grade fever, ascites with mild or absent abdominal pain, and peritoneoscopic findings of inflammation in this case speciously simulated tuberculous peritonitis. The presentation of tuberculous peritonitis can be subtle, with intermittent low grade fever and mild or absent abdominal pain.[3,4] Although the peritoneal fluid in tuberculous ascites usually has a yellow color, a total protein level exceeding 3.0 grams per dl and a lymphocytosis of 80 percent or more,[3] both sanguineous ascites and a spectrum of lymphocyte counts in this condition are well documented.[5-7] A total protein content in ascitic fluid of less than 3.0 grams per dl is also not unusual,[4] especially in alcoholic persons with cirrhosis.[5] Although visually directed peritoneal biopsies might be expected to provide histologic confirmation of tuberculosis, they are often inconclusive and laparotomy is required to establish the diagnosis.[3] This appeared to be the problem in the present case. Before the discovery of free intraperitoneal gallstones during abdominal exploration, the diagnostic impression of the operating surgeon was tuberculous peritonitis.

The fact that massive amounts of bilious ascites can be clinically asymptomatic is unusual, but well described.[8,9] It is this uncommon feature of the condition that delays its prompt diagnosis. Bile in the peritoneal cavity is almost always accompanied by severe abdominal pain and toxic shock with rapid exudation of fluid into the peritoneal space. However, the insidious and asymptomatic accumulation of bilious ascites has been produced experimentally when bile entering the peritoneal cavity is sterile.[10-12] The intense bile staining in the subhepatic space suggests that the bile leakage from the spontaneous rupture of the gallbladder wall was confined, resulting in the slow accumulation of bile in the remainder of the peritoneal cavity. It may be speculated that absence of a rise in the serum bilirubin level, which may accompany prolonged bilious ascites, was not seen in this patient because of the small rate of bile entering the abdominal cavity.

A bile leak is rarely considered in the differential diagnosis of ascites, particularly in the absence of

an acute disorder within the abdomen. However, the asymptomatic form has been described following a surgical procedure,[13] trauma,[14] percutaneous cholangiography[8] and liver biopsy,[9] and spontaneous rupture of the extrahepatic biliary tree in infants and children.[15] In addition to being the first report of bilious ascites due to spontaneous rupture of the gallbladder wall, this case is a poignant reminder that it is necessary to demand appropriate confirmation of the diagnosis of extrapulmonary tuberculosis. The case also calls attention to the expedience of using a dipstick to assess the presence of bilirubin in ascitic fluid while awaiting confirmatory biochemical analysis. Because bilious ascites can clinically and biochemically simulate infectious peritonitis, it should be considered in the differential diagnosis of newly asquired progressive ascites, with or without fever.

Summary

The combination of fever, weight loss, painless ascites and a positive tuberculin skin test suggested the diagnosis of peritoneal tuberculosis in a 60-year-old man with a history of alcoholism. Clinical and laboratory studies were consistent with the diagnosis but results of peritoneal biopsies were inconclusive. An exploratory laparotomy was therefore carried out and surprisingly showed an occult perforation of the gallbladder wall, resulting in asymptomatic bilious ascites. The case points to the need to definitively diagnose the cause of ascites before initiating therapy.

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Refer to: Heyman MB, Paterno VI, Ament ME: *Campylobacter* colitis: A cause of chronic diarrhea in children. West J Med 1982 Sep; 137:243-245

Campylobacter Colitis

A Cause of Chronic Diarrhea in Children

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INFECTION BY *Campylobacter jejuni** has been described as a gastroenteritis,[1-5] with pathologic involvement of the jejunum and ileum, that spares the colon.[2,6] In the past two years, however, several cases of adult patients with acute *Campylobacter* colitis have been reported.[7-11] *Campylobacter* colitis has not been previously reported in children.

A 7-month-old girl with chronic diarrhea producing blood-streaked feces and a 13-year-old girl with crampy abdominal pain and bloody diarrhea are reported to document the existence of chronic *Campylobacter* colitis in infants and children and its response to treatment.

Reports of Cases

CASE 1. A 7-month-old female infant was seen with a two-month history of diarrhea. Her stool frequency had increased from the usual one to two yellowish green formed stools to six to eight watery stools per day.

A week after the onset of diarrhea, the feces contained bright red blood with mucus. Cultures of stool specimens were negative for *Salmonella* and *Shigella* and a leukocyte count showed a leukocytosis. The patient responded to a milk protein-free formula, Pregestimil (Mead Johnson Nutritional Division, Evansville, Indiana), and the diarrhea and blood in the feces ceased. Ten days later, her fecal output increased and became

*This has recently been upgraded from *Campylobacter fetus* subspecies *jejuni* to a separate species.

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bloody for the second time. Treatment with half-strength soybean formula for a month as an outpatient, followed by peripheral vein total parenteral nutrition as an inpatient, was unsuccessful in stopping the blood-streaked diarrhea. Eight weeks into her illness she had her first fever and was transferred to UCLA Hospital, Los Angeles.

Her height was 70.5 cm (75th percentile) and weight was 7.32 kg (40th percentile). The findings on physical examination were normal. Laboratory studies showed the following values: serum sodium 142 mEq per liter, serum chloride 106 mEq per liter, serum bicarbonate 16.4 mEq per liter (normal 23 to 29), serum aspartate aminotransferase (AST, formerly SGOT) 41 IU per liter (normal 6 to 36), serum alanine aminotransferase (ALT, formerly SGPT) 11 IU per liter (normal 10 to 45), serum protein 6.6 grams per dl and serum albumin 4.1 grams per dl. Analysis of urine was normal. Hemoglobin was 11.2 grams per dl, hematocrit 33.6 percent; leukocyte count was 10,500 per cu mm, with 10 percent segmented neutrophils, 2 percent band forms, 74 percent lymphocytes and 8 percent monocytes; platelet count was 490,000 per cu mm. Admission stool specimen examination showed five to six leukocytes and erythrocytes per high-powered field; all stool specimens had a normal pH of 6.5 and were read as negative with Clinitest and Hematest (Ames Company, Inc.). Proctosigmoidoscopic examination showed punctate ulcerative lesions extending the entire 10 cm examined; however, areas of normal vascular pattern were seen adjacent to spontaneously friable mucosa. Rectal valves were edematous. Rectal suction biopsy specimens showed acute and chronic colitis. Cultures of a stool specimen from the proctosigmoidoscopic examination grew *C jejuni* and were negative for other enteric pathogens. She was treated with administration of erythromycin ethylsuccinate, 50 mg per kg of body weight per day for ten days. The stool frequency decreased to one a day, and the stool specimens became free of erythrocytes and polymorphonuclear leukocytes. Culture of a stool specimen was repeated a week after completing a course of antibiotic medications and did not grow *Campylobacter*.

CASE 2. A 13½-year-old girl had crampy lower abdominal pain for a week and a half. Three days after the onset of the cramps, she had three red, mucoid stools. The cramping episodes occurred four to five times a day. The maximum temperature recorded was 38°C (100.5°F). Administration of Donnatal (hyoscyamine sulfate, atropine sulfate, scopolamine hydrobromide and phenobarbital) and Hycodan (hydrocodone bitartrate and homatropine methylbromide) did not relieve her symptoms. With each episode of cramps, she had a bowel movement of a small amount of diarrheal feces that, on microscopic examination of a specimen, showed sheets of polymorphonuclear leukocytes. She was admitted to UCLA Hospital because of the severity of cramps, weight loss of 3 kg and persistence of diarrhea.

Height was 146 cm (below the fifth percentile) and weight was 30.5 kg (below the fifth percentile). The patient had a flat abdomen with increase in bowel sounds and diffuse abdominal tenderness with guarding. The results of the rectal examination were normal and the remainder of her physical examination elicited no abnormalities. Significant laboratory findings included a leukocyte count of 7,700 per cu mm with 64 percent segmented neutrophils, 28 percent band forms and 8 percent monocytes. Proctosigmoidoscopic examination showed spontaneous friability of the rectal mucosa to 18 cm, with a general loss of vascular pattern. A stool specimen taken during this examination grew *C jejuni*. Her condition gradually improved in the third week of her illness without antibiotic therapy, and pain ceased in the fourth week. Repeat culture of a stool specimen was negative for the organism.

Discussion

Infection caused by *C jejuni* has been typically described as an acute gastroenteritis presenting with symptoms of fever, abdominal pain and diarrhea, often with bright red blood.[1-4] Infants and children who have a history of diarrhea of longer than 14 days ("chronic diarrhea") and colitis should still be considered to have an infectious diarrhea until cultures of stool specimens are reported negative for *Campylobacter, Shigella, Salmonella* and *Yersinia*.

The diarrhea associated with proved *Campylobacter* gastroenteritis usually lasts from one day to three weeks, though reports suggesting chronic infection exist.[6,12] Three cases of prolonged diarrhea have been reported associated with isolation from blood culture of "*Vibrio*-like" organisms, now reclassified as *Campylobacter* organisms. Wheeler and Borchers[6] reported the cases of two siblings, an 11-month-old infant and a 4-year-old child, with nine-month histories of four to five episodes of diarrhea. Culture of a blood

specimen from the infant grew *Vibrio* and the sibling had a positive hemagglutination titer to the same *Vibrio*. Both responded to treatment with streptomycin sulfate. Another case of "related *Vibrio*" cultured from a blood specimen was reported by Cadranel and co-workers[12] in a 16-month-old child who had recurrent diarrhea for five months.

The absence of malabsorption in our cases implies limited or absent mucosal damage to the small bowel, wherein this organism has been cultured in previous reports.

Ulcerative colitis or Crohn's disease should only be diagnosed after the presence of enteric pathogens and parasites is ruled out, typical histologic evidence is obtained or classical findings of ulcerative colitis or Crohn's disease are seen in barium enema studies. The findings of leukocytes and blood in the feces, colitis with inflamed friable mucosa on sigmoidoscopic examination, and inflammatory reaction with crypt abscesses and mucus depletion on histologic examination of rectal biopsy specimens are similar to that of adult cases of *Campylobacter* colitis.[7-10] One 14-year-old pediatric patient with similar pathologic findings has been described who had a barium enema study showing pancolitis; symptoms resolved after treatment with erythromycin.[7] As suggested previously,[7-10] a first attack of "ulcerative colitis" that does not later recur may in some cases actually be an infectious disease caused by *C jejuni*.

Erythromycin proved to be an effective antimicrobial agent and is considered one of the drugs of choice for treatment of *Campylobacter* infections. Relapses have not been reported to occur after treatment with this medication.[1] Other antibiotics with high activity against *C jejuni* include gentamicin, chloramphenicol, furazolidone and the tetracyclines.[13]

In summary, two cases of chronic colitis caused by *C jejuni* are presented. Physicians caring for children should consider *Campylobacter* enterocolitis in the differential diagnosis in infants with chronic diarrhea, especially if gross blood is present in the feces. A sigmoidoscopic examination would be helpful in obtaining stool specimens for isolation of pathogenic organisms and for evaluating a patient with bloody diarrhea. However, a fresh stool specimen is adequate for the diagnosis of *C jejuni*, if cultured appropriately.

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Transient Bifascicular Block Following Blunt Chest Trauma

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ALTHOUGH CONDUCTION DEFECTS caused by blunt chest trauma are probably not rare, well-documented cases have been reported infrequently. Dolara and Pozzi[1] in 1966 reviewed 23 cases of trauma-related atrioventricular (AV) block reported between 1912 and 1938. Only a few met most or all of the following criteria: youthful age, absence of preexisting heart disease, great magnitude of injuring force, repolarization changes on electrocardiograms suggestive of associated myo-

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cardial involvement, associated heart lesions (such as valvular, pericardial or septal lesions), brief interval between the trauma and the discovery of the conduction defects and absence of trauma-induced hyperkalemia. Thus they concluded that only three cases of AV block,[2-4] ten cases of right bundle branch block[5-9] and two cases of left bundle branch block[2-8] were proved to be due to trauma.

Since 1966 there have been four reported cases of atrioventricular block,[10-12] nine reported cases of right bundle branch block[12-18] and two cases of nonspecific intraventricular conduction delay[19,20] that have met most or all of the above-mentioned criteria.

We report an additional case of transient post-traumatic bifascicular block that has each of the associated features described by Dolara and Pozzi in 1966.[1]

Report of a Case

History

A previously healthy 17-year-old adolescent was thrown against the left car door and steering wheel when his automobile slid off a wet road and struck a pole while traveling at 50 miles an hour. He did not lose consciousness. When he arrived at the emergency room an hour later, he had pleuritic-type chest pain, left precordial pain, lower abdominal pain and left hip pain.

He had suffered a cerebral concussion six years before but there were no sequelae. There was no history of any cardiac abnormality and previous physical examinations showed no abnormalities. Results of a prior hemoglobin electrophoresis study were normal.

Physical Examination

The patient appeared lethargic but was communicative. His pulse rate was 85 beats per minute and he did not have a pulsus paradoxus. The blood pressure, taken with the patient supine, was 96/52 mm of mercury. Respirations were 20 per minute and appeared unlabored. There were abrasions and glass splinters on both cheeks. No external signs of thoracic trauma were noted but he had pain on compression of the sternum and left precordium. There was no crepitus heard and breath sounds were normal. The jugular venous pulse could not be seen; the carotid upstrokes appeared normal. The apical impulse, though indistinct, was noted between the fourth and fifth intercostal spaces in the left midclavicular line. There was mild hyperactivity and a systolic thrill along the left sternal border but no heave. S1 was normal and S2 was physiologically split. There was a grade 4/6 three-component friction rub heard at the left sternal border that made a crunching sound during systole and was loudest during inspiration. No gallops or murmurs could be heard. Mild abdominal distention was noted and bowel sounds were diminished. Tenderness and guarding were elicited by palpation of the pelvis and the left olecranon process. Guaiac test of a stool specimen was negative. Lavage of the peritoneum with saline showed gross blood.

Laboratory Findings

Results of electrolyte studies were normal and the hematocrit was 37 percent. The patient had gross hematuria but there were no clots or casts in the urine. Arterial blood gas determinations made while the patient was breathing room air were as follows: pH 7.41, oxygen partial pressure (Po_2) 69 mm of mercury and carbon dioxide partial pressure (Pco_2) 39 mm of mercury. X-ray studies of the chest showed no abnormalities but bone films showed fractures of the right pubic ramus and left olecranon. Intravenous pyelography and cystography showed mild left ureteral deviation only. The electrocardiogram (ECG) (Figure 1, day 1) showed sinus tachycardia, right bundle branch block and anterosuperior fascicular block (left anterior hemiblock).

Hospital Course

With intravenous administration of fluids, the patient's blood pressure rose to 124/84 mm of mercury and the central venous pressure to 8 cm of water. At exploratory laparotomy, a ruptured spleen was removed and a hepatic laceration repaired. The fracture of the olecranon was then internally fixed.

The patient was extubated 14 hours after the surgical procedure and no hypoxemia or dysrhythmias were detected. On day 2 (Figure 1) the electrocardiogram still showed right bundle branch block but the left axis deviation was not as pronounced and T-wave inversion developed in leads II, III and aV_F, suggestive of an inferior wall contusion. Other laboratory values were as follows: serum creatine kinase (CK), greater than 1,200 units; serum lactate dehydrogenase (LDH), greater than 500 units, and serum aspartate amino transferase (AST, formerly SGOT), 247 units. The CK-MB fraction was 4.7 percent (up-

per limit of normal was 3 percent) and the LDH_1 fraction was greater than LDH_2. The pericardial friction rub had decreased in intensity.

On day 5 the conduction disturbances had resolved (Figure 1) but the ECG continued to show evolution of inferior T-wave inversion. The friction rub was absent but a grade 3/6 holosystolic murmur was appreciable. An echocardiogram (Figure 2) showed no abnormalities except for possible early systolic mitral valve prolapse. Results of a radionuclide scan on day 6 using technetium Tc 99m pyrophosphate were normal.

In the latter part of his hospital course, the patient noted occasional episodes of nonexertional, sharp left precordial pain that usually lasted about a minute and resolved spontaneously. He noted no dyspnea. He was discharged on day 12 with a stable holosystolic murmur.

Follow-up 18 months later found that he was athletic and had no specific cardiovascular symptoms. On physical examination he was noted to have a precordial systolic thrill and a grade 4/6 holosystolic murmur. An electrocardiogram showed only early repolarization in the left lateral leads, a normal variation. An echocardiogram (Figure 3) showed pansystolic mitral valve prolapse. Cardiac catheterization showed normal pressures, trivial mitral regurgitation and

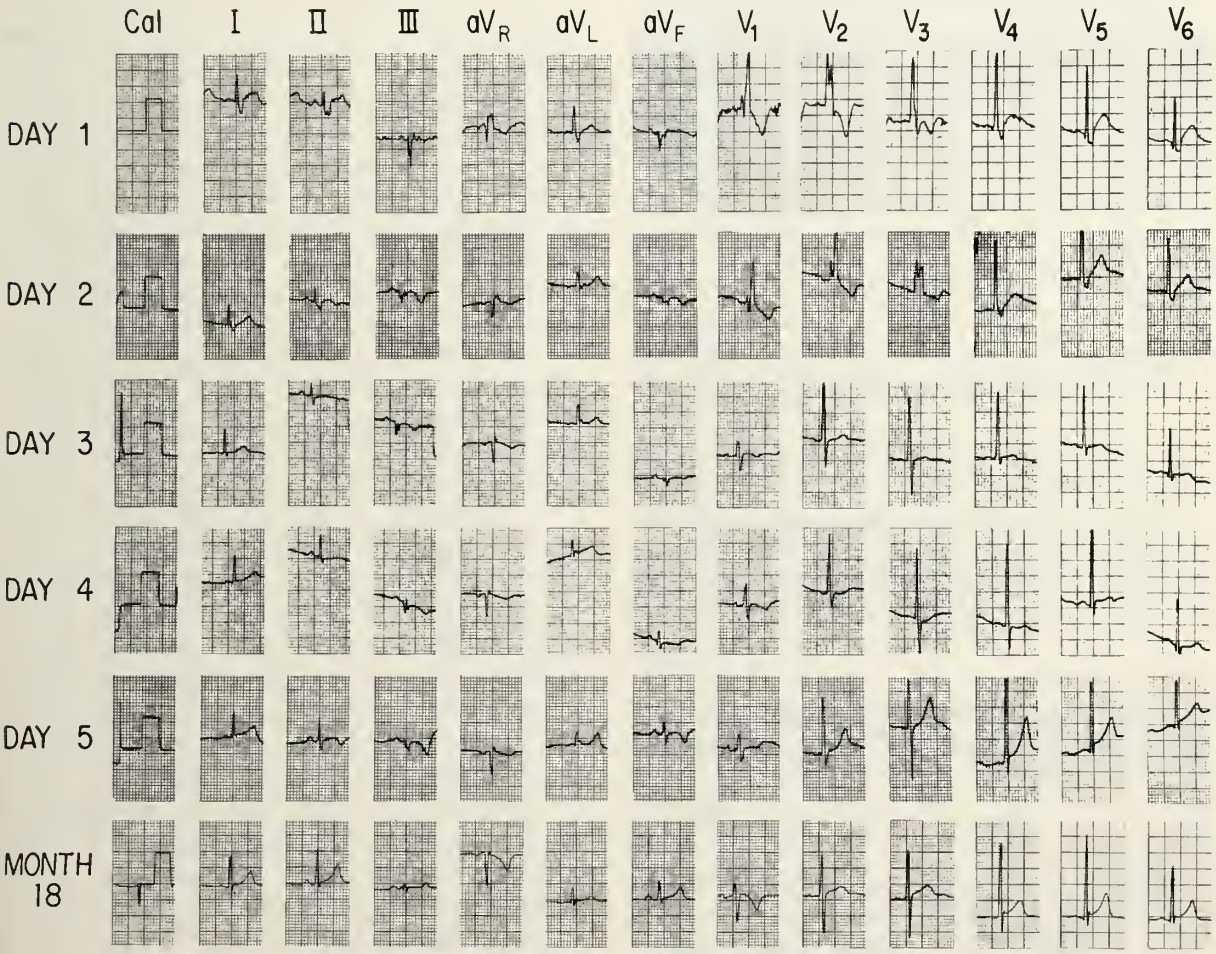

Figure 1.—Serial electrocardiograms of a 17-year-old adolescent who suffered blunt chest trauma causing transient bifascicular block and an inferior wall myocardial contusion. **Day 1** was taken on admission and showed right bundle branch block and left axis deviation suggesting bifascicular block. **Day 2** shows that the terminal QRS forces are slightly less superior but evidence of bifascicular block persists. The T waves in leads II, III and aV_F have inverted. **Day 3** shows that the right bundle branch block has resolved and the QRS axis is about −30 degrees. T-wave inversions persist in leads III and aV_F and there is early precordial transition suggestive of posteroinferior wall injury. **Day 4** shows progression of the same pattern. **Day 5** shows deepening of the T-wave inversions in leads II, III and aV_F. **Month 18** is a follow-up tracing done 18 months after the trauma while the patient was asymptomatic. It shows early repolarization, a normal variant pattern, in leads I, II, aV_L and leads V2 through V6. There is no evidence of residual conduction defect or myocardial contusion. Cal = 1 mV calibration.

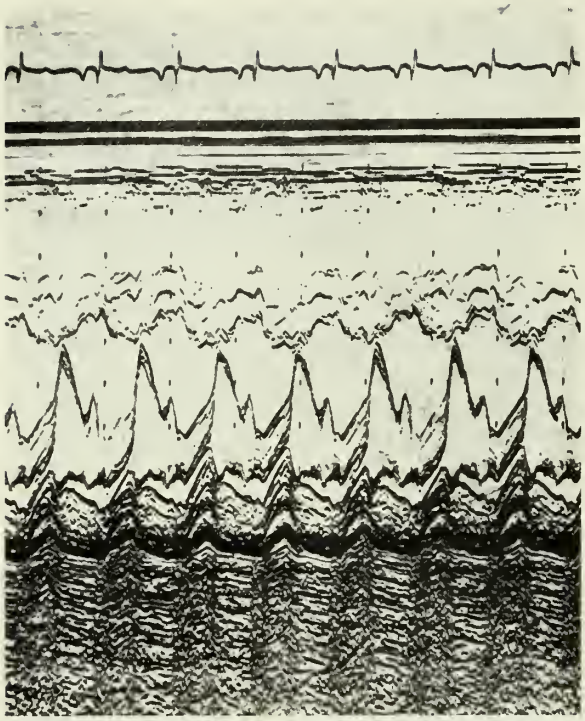

Figure 2.—An echocardiogram of the patient's mitral valve shortly after the accident. It appears normal except for the suggestion of early systolic mitral valve prolapse.

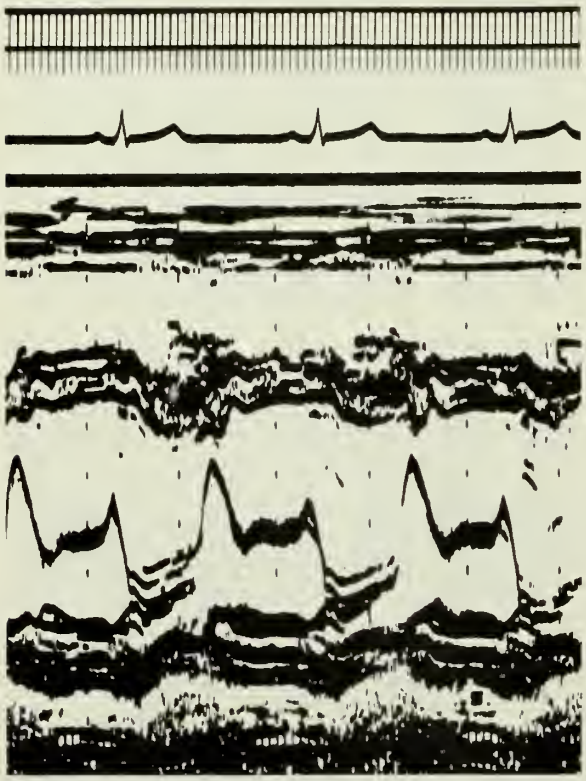

Figure 3.—A follow-up echocardiogram done 18 months after the first shows pansystolic mitral valve prolapse.

prolapse of the posterior leaflet of the mitral valve. The left ventricular wall motion was normal on a biplane left ventriculogram.

Discussion

No electrocardiogram had been done before the patient's trauma. Nonetheless, it is certain that the transient bifascicular block in our patient was caused by trauma. Hypoxia or heart rate, electrolyte or acid-base disturbances could not account for the conduction abnormalities. Before his chest injury, he was an asymptomatic athletic adolescent who had no known heart disease and no murmurs. The echocardiogram done following the injury showed no mitral valve abnormalities except for possible early systolic mitral valve prolapse (Figure 2). The trauma was of sufficient magnitude to cause hepatic and splenic rupture and multiple fractures. In addition to the transient conduction defects, inferior repolarization changes developed with all the features of a myocardial contusion and there was enzymatic evidence suggestive of myocardial necrosis. The radionuclide scan done six days after the trauma showed no abnormalities. This is not surprising, however, considering reports that in experimentally traumatized dogs and in eight patients with blunt chest trauma radionuclide scans showed abnormalities only as late as 96 hours after the trauma.[21,22] All the scans done six days or more after the injury gave normal findings.

A holosystolic murmur was appreciable several days after the trauma. Whereas the first echocardiogram showed minimal evidence of mitral valve prolapse, the second, done 18 months later, showed pansystolic mitral valve prolapse. The left ventriculogram showed prolapse of the posterior leaflet associated with one plus mitral regurgitation. While it is possible that the prolapse was due to congenital myxomatous degeneration, this is unlikely, as a murmur had not been detected on previous physical examinations. The murmur was grade 4/6 and did not respond to maneuvers affecting left ventricular filling. The electrocardiographic and enzymatic evidence of an inferior myocardial contusion and the evidence of prolapse of the posterior mitral valve leaflet make it almost certain that posterior papillary muscle dysfunction occurred as a result of trauma.

The findings in our patient met all of the criteria for trauma-induced heart disorder proposed by Dolara and Pozzi[1] in 1966. This case illustrates some important features of this disorder.

Pathologic Changes

Pathologic changes associated with trauma-induced conduction disturbances are variable. Kissane and co-workers[23] often found no pathologic changes at all in experimentally traumatized dogs, despite findings of repolarization changes, conduction defects and dysrhythmias. They speculated that the conduction defects were due to edema. Borisenko[24] called this phenomenon "concussion." Areas of myocardial hemorrhage ("contusion") were also found but were variable in the way in which they corresponded to electrocardiographic findings. Indeed, in a recent clinical series of patients with blunt chest trauma, abnormal changes developed on the electrocardiograms of 63 percent of the patients, but only 14 percent had enzymatic evidence of myocardial necrosis.[25] Parmley and associates[7] reviewed 546 autopsies of patients with blunt injury of the myocardium. One fifth of the significant pathologic lesions comprised cardiac contusions and myocardial lacerations and were the only lesions correlated with a prolonged survival. In only 12 of those cases was the cardiac lesion primarily responsible for immediate death.

Natural History of Posttraumatic Conduction Defects

In nearly all of the cases in which follow-up was reported the conduction defects were—as in our patient—transient, lasting only hours to days. One patient required pacemaker placement for transient complete heart block that eventually evolved to transient Mobitz I second degree block.[10] In three of the nine reported cases of right bundle branch block, left axis deviation was also present, suggesting anterosuperior fascicular involvement as well.[15,17] Reports of posttraumatic left bundle branch block or left posterior fascicular block are extremely rare, probably because the left posterior fascicle is larger, less discrete and located more posteriorly in the septum.

Experimental studies confirm that blunt chest trauma can cause conduction defects and that these defects are usually transient.[23,24,26] In the animal studies of Kissane and associates,[23] conduction defects developed only in the dogs that received the strongest blows. Also, dysrhythmias and cardiac arrest were more likely to occur in the dogs subjected to the most severe trauma.

In the cases of posttraumatic conduction defects that have come to clinical attention, the prognosis is very good if there are no complicating cardiac lesions. Although angina or dyspnea can develop late, recovery is usually rapid and complete.[26-28]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

The Ash Babies Never Came

To the Editor: Crisis breeds procreation, or so one would conclude from reports on the aftermath of disasters such as the 1965 Northeast power blackout. Hospital personnel report being swamped by mothers delivering babies nine months after such events occur. For this reason, we expected Washington state residents to have a relatively large number of babies on or about February 18, 1981, nine months after the famous May 18, 1980, Mount St Helens eruption. In fact, the February 19, 1981, edition of the Seattle *Post-Intelligencer* reported just such an occurrence for certain Eastern Washington and Idaho hospitals.

In order to establish the existence or extent of this increased birth rate, we compared 1980 and 1981 birth data. For the analysis, the state was divided into three geographical areas: (1) eastern Washington counties affected by the ashfall (Adams, Grant, Kittitas, Lincoln, Spokane, Whitman and Yakima), (2) western Washington counties affected by the ashfall (Cowlitz, Lewis and Skamania) and (3) all other Washington counties. Three time periods were considered: (1) normal gestation, 38 to 42 weeks after May 18, (2) an intermediate period, one week before and one week after normal gestation, and (3) the remainder of the year. We expected that, during the normal gestation period, the ashfall counties would show an increase in deliveries or a larger percentage of statewide deliveries. However, we found no significant differences ($P>0.29$), comparing this time period either with other time periods in 1981 or with the same time period in 1980. Thus, the expected deluge of "ash babies" does not appear to have occurred.

How can these results be reconciled with those described in reports previously mentioned? The effect of disaster on the birth rate has never been documented by a systematic study. Most reports, both for this event and other disasters, are based on subjective evidence—that is, hospital personnel noticing a large number of babies being born. In reality, they may only be seeing the normal day-to-day variation in numbers of births. For example, in eastern Washington ashfall counties during the gestation period, the number of births per day ranged from 19 to 46; individual hospitals probably have even greater fluctuations. The temptation is great to attribute these fluctuations to a cause, particularly when one is as readily available and publicized as the "ash babies."

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Editor's Note: There may be something special about a long blackout in early evening. —MSMW

Pacilepsy

To the Editor: Parents and other counselors of youth, seeking additional arguments against video games, should know that they can contribute to convulsions.

On a recent Saturday at Lake Berryessa, California, a previously well 25-year-old man spent the day water-skiing and drinking seven bottles of beer. By evening he was mildly fatigued but without complaint, as he played Pac-Man in a friend's trailer. Suddenly and without aura he had an observed generalized convulsive seizure. Mild muscle soreness persisted for several days, but he otherwise remained well and did not seek medical attention until four days after the episode. At that time complete examination showed only a slight elevation of alanine aminotransferase (serum glutamic-pyruvic transaminase). An electroencephalogram was normal.

Undue sensitivity to photic stimulation is characteristically seen during an abstinence period in patients addicted to sedating drugs such as alcohol, and I presume that a similar mechanism was

operative in this man. The transaminase elevation indicated a greater alcohol intake than admitted, and a day of unusual activity may have enhanced his vulnerability. In the setting of a darkened twilight room, his concentrating on the flashing lights of a video game was enough to initiate the seizure.

Suitable admonitions were offered concerning the proper mixing of alcohol with Pac-Man.

MARTIN TERPLAN, MD
San Francisco

Acronyms in Medical Papers

To the Editor: Something irritates me. I suspect I am not the only MD who feels this way. It may be a hidden reaction in many, like it was in those who could not see the emperor's clothes. Those little groups of letters irritate and frustrate me (acronyms). Maybe I am a slow learner, but they slow down my reading and comprehension when scanning a medical paper. I have to stop and look back a few lines, often, to recall what they mean. By the time I've finally caught on to all the cute little groups, the material ends, and I've got a new batch to learn for the next paper. I wonder if I am alone in this feeling, or if others have feelings like mine.

Are acronymical contractions supposed to save time and facilitate comprehension? They fail to do it for me.

I'd like to hear feedback from some of the readers of the journal. My local colleagues agreed with me last time when we discussed it at lunch.

ALFRED G. ROBINSON, MD
Camarillo, California

Comments on Ethical Protocol

To the Editor: In applying the protocol developed in the July article on ethical problems,[1] the first paragraph on "contracts" seems overly simplistic. Perhaps the primary doctor-patient relationship "contract" is indeed with the child rather than the parents, but it seems unreasonable and unethical to totally eliminate the parents from contractual consideration. The needs, desires and capacities of the parents deserve consideration not only for the sake of the parents but also for the sake of the child. On this basis alone the conclusion that the physician should intervene with the courts might well be wrong.

Furthermore, the first "general assumption" is open to question in terms of the specific case and in general. The "interventionist philosophy" that has dominated medical education and medical standards for a good many years seems to lead most physicians to equate more with better and most with best—that is, the more diagnostic procedures and the more therapeutic interventions that can be justified, on any basis, the better the care. This, despite a very large and convincing body of literature clearly demonstrating that more is often not better but worse and is more than occasionally dangerous to the patient.

It would seem to be the conclusion of the authors that surgical treatment of duodenal atresia in order to preserve the life of a child with Down's syndrome is best for the child, and it might be. However, it is not at all difficult to imagine a scenario of multiple complications following surgical procedures preserving the life of a baby with Down's syndrome with a very low IQ left to be the economic and human responsibility of parents who, wanting no part of such responsibility and angry at having it forced on them, abuse the child, resulting in long-term morbidity and perhaps mortality. Is that really best for the child?

While the guidelines presented in the article may be helpful to physicians, in the individual case much finer judgments are called for. There is considerable doubt that modern medical education is providing the basis for such insights by young physicians. And most of us who are older did not get it during our education nor have many developed it over our years of practice. Perhaps a follow-up article in greater depth is indicated.

MARVIN J. SHAPIRO, MD
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REFERENCE

1. Watts MSM, Bayley C, Healy FA, et al: Ethical problems in medical practice—A protocol for the guidance of physicians (Medical Ethics). West J Med 1982 Jul; 137:83-86

* * *

To the Editor: The article "Ethical Problems in Medical Practice" by Watts and colleagues[1] is an interesting exercise in establishing theoretical ethical guidelines, but in practice I would find it of little help, as an examination of the case example presented reveals.

The authors chose the difficult and provocative case of a child with Down's syndrome with a single, correctable gastrointestinal lesion. They used their law of "mutual trust" and imply that it is clear that if the law is applied, a physician will choose to intervene surgically. I submit this is not the case, necessarily.

Suppose I, as an ethical physician, believe that

the quality of the patient's life will be very questionable and therefore believe that the operation proposed is not in the patient's best interest. Further, suppose that I believe that death is merely a part and continuation of life and not to be fought off at all costs. I can then apply a law of "mutual trust" and allow the patient to die. In short, how I apply the rule depends on what *I* define as "in the best interest of the patient." As long as my conscience is clear, I can logically opt for or against the proposed operation.

Alas, the formulation of ethical rules in the end makes little difference. What does matter is the beliefs of the people who apply them.

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REFERENCE

1. Watts MSM, Bayley C, Healy FA, et al: Ethical problems in medical practice—A protocol for the guidance of physicians (Medical Ethics). West J Med 1982 Jul; 137:83-86

* * *

To the Editor: I was delighted to see the article "Ethical Problems in Medical Practice"[1] in the last issue. These aspects deserve the attention they recently have been receiving. The protocol you and your coauthors presented is both practical and useful. However, I must take issue with the application of it that occurred in your case study. In simplifying the problem, I believe you introduced error and arrived at a conclusion that is by no means universally acceptable or certain. Let me explain.

The *Rule of Mutual Trust* and the *Golden Rule* are conceptually separate and distinct but practically inseparable and largely overlapping. No professional can arrive at an opinion or belief as to the best interest of the patient except from the reference point of his or her own personal philosophy and beliefs. This may in some cases be interconnected with the *Religious Rule* whenever and to the extent the personal beliefs of the professional are determined by the professional's religious convictions. Thus, in my opinion the Golden Rule *always* applies and the Religious Rule often applies whether we recognize it or not. With this understanding my conclusion differs from that of the committee that acted in your case study.

It is my belief that an unwanted child is doomed to a miserable existence and that this is specially so if the child is handicapped. It is further my belief that *human life* as opposed to biologic life implies self-consciousness and the ability to influence and control, at least to some extent, one's environment. That belief includes the concept that quality of life affects the value of life and that sometimes, under some circumstances, death is preferable. This belief does not mean that I devalue life or deny the sanctity of life. It does mean that I deny that biologic existence under any and all circumstances is the ultimate and immutable value.

Had I been caring for this child and its parents I would have honored their decision.

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REFERENCE

1. Watts MSM, Bayley C, Healy FA, et al: Ethical problems in medical practice—A protocol for the guidance of physicians (Medical Ethics). West J Med 1982 Jul; 137:83-86

Refer to: McPhee SJ: The evaluation of anemia (Topics in Primary Care Medicine). West J Med 1982 Sep: 137:253-256

Topics in Primary Care Medicine

The Evaluation of Anemia

STEPHEN J. McPHEE, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

ANEMIA is a common problem in primary care practice, occurring with an annual incidence of 18 cases per 1,000 patients. Because anemia is a sign of underlying disease and usually not a primary disease itself, the clinician must diligently search for a cause before considering therapy. The diagnostic evaluation of anemia is complicated by the wide range of possible causes and the large number of diagnostic tests and procedures available. Nonetheless, most patients presenting with anemia have a readily detectable illness and evaluations can be done without admitting them to hospital.

From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, School of Medicine.

Supported in part by the Robert Wood Johnson Foundation and the John A. Hartford Foundation.

Reprint requests to: Stephen J. McPhee, MD, Division of General Internal Medicine, 400 Parnassus Avenue, Room A-405, University of California, San Francisco, San Francisco, CA 94143.

Definition of Anemia

Anemia is defined in terms of mean hematocrit and hemoglobin levels adusted for age, sex and altitude. For an adult man at sea level, the normal hemoglobin concentration is approximately 16 grams per dl (range 14 to 18 grams) and the normal hematocrit is 47 percent (range, 42 to 52). For an adult woman, the normal hemoglobin concentration is 14 grams per dl (range, 12 to 16) and normal hematocrit is 42 percent (range, 37 to 47). At higher altitudes, normal hemoglobin

values are slightly higher, increasing roughly in proportion to the elevation above sea level.

Diagnostic Evaluation of Anemia

History and Physical Examination

A thorough history can uncover predisposing factors for anemia, such as inadequate diet, excessive alcohol intake, or drug or toxin exposure. The history may provide clues to the underlying cause. For example, the patient's ethnic background or family history may suggest a chronic hemolytic anemia. In addition, the history helps to determine the impact of the anemia on the patient. Thus, the history explores for symptoms of anemia. These, of course, depend more on the age of the patient, the presence of other disorders that limit cardiopulmonary compensation, the rate of development of anemia and the underlying cause than on the absolute level of the hematocrit.

Similarly, the physical examination of an anemic patient has several objectives. First, through measurement of orthostatic changes in the pulse rate and blood pressure, it allows rapid assessment of the patient's blood volume. Second, examination of the skin, oronasopharynx, abdomen, vagina and rectum and testing the stool, urine and, in some cases, nasogastric aspirate for blood help to exclude active bleeding. Third, it may provide physical clues to the underlying cause. Finally, examination for signs of shock or congestive heart failure helps to determine the patient's response to the anemia.

Laboratory Studies

The basic laboratory evaluation of the anemic patient consists of (1) a complete blood count, including hemoglobin and hematocrit levels, leukocyte count, erythrocyte indices and platelet count or estimate, (2) a Wright-stained smear of peripheral blood and (3) a reticulocyte count. The reticulocyte index must then be calculated to correct for the degree of the anemia and the longer life span of younger retriculocytes in severe anemia according to the formula:

$$\text{reticulocyte index} = \frac{\text{reticulocyte count}}{\text{maturation time}} \times \frac{\text{actual hematocrit}}{\text{normal hematocrit}}$$

The maturation time varies inversely with the hematocrit; it is 1.0 for a hematocrit of 45 percent, 1.5 for 35 percent, 2.0 for 25 percent and 2.5 for 15 percent. The normal value for reticulocyte count and reticulocyte index is 1 percent.

Further laboratory studies depend upon the initial classification of the anemia.

Classification of Anemia

Anemias may be classified according to erythrocyte morphology. Using the peripheral smear and the erythrocyte indices, the physician can classify every anemia into one of three morphological categories: (1) microcytic-hypochromic anemias, (2) macrocytic anemias and (3) normocytic-normochromic anemias.

Microcytic-hypochromic anemias are characterized by (1) peripheral smear findings of small erythrocytes (as compared with the nucleus of a small lymphocyte) with an increased central pallor and (2) erythrocyte indices with a mean cell volume below 82 cu μm and a mean cell hemoglobin concentration below 31 grams per dl. Macrocytic anemias are characterized by (1) the peripheral smear findings of large, sometimes oval erythrocytes and (2) erythrocyte indices with a mean cell volume above 100 cu μm and a normal mean cell hemoglobin concentration between 31 and 34 grams per dl. Normocytic-normochromic anemias are characterized by (1) the peripheral smear findings of normal erythrocytes and (2) erythrocyte indices with a normal mean cell volume between 82 and 100 cu μm and a normal mean cell hemoglobin concentration between 31 and 34 grams per dl.

Table 1 lists the common causes of anemia according to this classification by erythrocyte morphology.

Microcytic-Hypochromic Anemias

The common causes for microcytic-hypochromic anemias include iron deficiency, thalassemia, hemoglobinopathies, sideroblastic and some chronic disease anemias. Differential diagnosis is aided by determination of the serum iron (Fe), total iron-binding capacity (TIBC), and percent iron-binding saturation (Fe/TIBC $\times$ 100), or by determination of the serum ferritin level.

Ferritin is an iron-storage protein. The serum ferritin level reflects the amount of ferritin in the storage pool, and thus offers a noninvasive evaluation of the body's iron stores. Normal serum levels, as measured by radioimmunoassay, range from 12 to 300 ng per ml. Serum ferritin is depressed in iron deficiency, elevated in chronic diseases such as Hodgkin's disease and liver disease, and may be normal if iron deficiency and chronic disease occur simultaneously. Although

TABLE 1.—*Classification of Anemia by Erythrocyte Morphology*

Microcytic-Hypochromic Anemia
(MCV<82 cu μm, MCHC<31 grams/dl)
Iron deficiency
Thalassemia
Hemoglobinopathy
Sideroblastic anemia
Chronic disease (some)
Macrocytic Anemia
(MCV>100 cu μm, MCHC 32-36 grams/dl)
Megaloblastic
B12 deficiency
Folate deficiency
Drug-induced
Nonmegaloblastic
Accelerated erythropoiesis
Acute hemorrhage
Acute hemolysis
Increased RBC membrane surface area
Chronic liver disease
Postsplenectomy
Myxedema
Marrow infiltration or failure
Normocytic-Normochromic Anemia
(MCV 82-100 cu μm, MCHC 31-34 grams/dl)
Acute hemorrhage
Acute hemolysis
Endocrine-metabolic disorders
Chronic disease (most)
Marrow infiltration or failure

MCHC = mean cell hemoglobin concentration; MCV = mean cell volume.

the serum ferritin is more specific than the serum iron and total iron-binding capacity, it is less sensitive, more expensive and generally less available.

In iron deficiency, the serum iron is usually decreased (below 40 μg per dl), the total iron-binding capacity normal or increased (above 410 μg per dl), and the percent iron-binding saturation depressed, usually below 15 percent; the serum ferritin is depressed, usually below 10 ng per ml. In the anemia of chronic disease, both the serum iron and total iron-binding capacity are decreased, resulting in a percent saturation that is normal or increased; in such cases, the serum ferritin level is usually increased above 300 ng per ml. In β-thalassemia, the serum iron, total iron-binding capacity, percent iron-binding saturation and serum ferritin levels are all normal. The diagnosis is suggested by the findings of a greatly decreased mean cell volume (often below 65 cu μm) out of proportion to the degree of anemia, an elevated erythrocyte number, target cells and basophilic stippling on smear, and an increased hemoglobin A2 concentration on hemoglobin electrophoresis. In sideroblastic anemia, the serum iron is normal or increased, the total iron-binding capacity normal or decreased, and the percent saturation normal or increased; the serum ferritin level is normal. Diagnosis depends upon bone marrow aspiration, which shows increased iron stores and ringed sideroblasts. Finally, in cases in which combined causes are suspected, such as iron deficiency and chronic disease, where percent iron-binding saturation or serum ferritin may be normal, bone marrow aspiration can be carried out; iron stores will be absent if iron deficiency is present.

Macrocytic Anemias

Macrocytic anemias include megaloblastic and nonmegaloblastic causes. Megaloblastic macrocytic anemias are due to inherited or acquired disorders of DNA synthesis, commonly mediated by vitamin B_{12} or folate deficiency. Nonmegaloblastic macrocytic anemias may be due to reticulocytosis following hemolysis or hemorrhage, to increased erythrocyte membrane surface area in hepatic disease or after splenectomy, to myxedema, or to myelophthisic, hypoplastic or aplastic anemias.

Differentiation of a megaloblastic from a nonmegaloblastic cause of macrocytic anemia is possible by further examination of the peripheral smear for hypersegmented polymorphonuclear neutrophils (strictly defined, more than 5 percent with five or more lobes) or by examination of the bone marrow aspirate for megaloblasts (enlarged erythrocytes precursors with excess cytoplasm and immature nuclei).

If a megaloblastic cause is suspected, a physician can choose between several diagnostic tests, each of which is problematic. Some rely upon fasting serum folate and vitamin B_{12} levels. Serum folate levels are altered by alcohol, drugs and diet, and therefore may not reflect true tissue deficiency. The erythrocyte folate level provides a better index of long-term intake and only slowly returns to normal after treatment with folate. It is more expensive, however, and may be low in vitamin B_{12} deficiency, because B_{12} is necessary for the utilization of folate by developing erythrocytes. Thus, the erythrocyte folate level does not distinguish easily between folate and vitamin B_{12} deficiency.

Similarly, serum vitamin B_{12} levels may be misleading. For example, they may be inappropriately low in patients with folate deficiency alone.

In addition, vitamin B_{12} levels determined by microbiologic assay may be falsely low in patients receiving antibiotic therapy. A potentially more serious shortcoming is that vitamin B_{12} levels determined by radioimmunoassay have been found to be normal in several patients with documented pernicious anemia.

The diagnosis of folate deficiency can best be established by a therapeutic trial of low doses of folate (200 μg per day), with careful monitoring of the reticulocyte count for response. High doses (greater than 1 mg per day) are not recommended because the diagnosis of pernicious anemia may then be masked by a nonspecific reticulocytosis. The diagnosis of vitamin B_{12} deficiency can be firmly established by the two-stage or dual-labeled oral Schilling's test. Because severe B_{12} or folate deficiency may cause clinically significant gastrointestinal malabsorption, however, the Schilling's test should be delayed until after therapy has been instituted.

Further definition of the causes of nonmegaloblastic macrocytic anemias begins with the reticulocyte index. This, if elevated, suggests hemolysis or hemorrhage; if depressed or normal, it suggests the possibilities of chronic liver disease, myxedema, marrow infiltration (myelophthisic anemias) or failure (aplastic anemias). If the history, physical examination, complete blood count and smear suggest myelophthisic or aplastic anemia, the physician should proceed directly to bone marrow biopsy for confirmation.

Normocytic-Normochromic Anemias

The many causes of normocytic-normochromic anemias fall into two general classes that can be separated by the reticulocyte index. Anemias due to rapid loss or destruction of erythrocytes have an elevated reticulocyte index. These include anemias due to acute hemorrhage and hemolysis. Anemias due to decreased production of erythrocytes by the bone marrow have a depressed reticulocyte index. These include anemias caused by endocrine-metabolic disorders, states of chronic infection, inflammation or neoplasia, and myelophthisic, hypoplastic and aplastic states.

Thus, if a patient with normocytic-normochromic anemia has an elevated reticulocyte index, the physician should first evaluate for acute hemorrhage. If no indication of hemorrhage is found, further evaluation for hemolysis is in order. Tests of serum bilirubin, lactic dehydrogenase and haptoglobin levels help to establish the diagnosis of hemolysis. Then, the physician may order erythrocyte glucose-6 phosphate dehydrogenase (G-6PD) level, Coombs' test and, in some cases, hemoglobin electrophoresis to pinpoint its cause.

If the reticulocyte index is normal or depressed, the physician should undertake a careful search for endocrine-metabolic disease (such as hypothyroidism, hypoadrenocorticism, panhypopituitarism, chronic renal failure or chronic liver disease) or for chronic infection, inflammation or neoplasm. Serum iron and total iron-binding capacity levels, if obtained, will both be depressed. If the reticulocyte count is severely depressed, or pancytopenia is present, the physician should proceed directly to bone marrow biopsy for confirmation of suspected myelophthisic, hypoplastic or aplastic anemia.

Bone Marrow Examination

Bone marrow aspiration, which allows assessment of cellular maturation and iron stores, is particularly useful in several circumstances. Iron deficiency can be diagnosed with certainty by iron stains of the marrow aspirate when peripheral smear, serum iron, iron-binding capacity or ferritin levels alone do not suffice for diagnosis. Sideroblastic anemia can be diagnosed only by showing iron granules ringing the nucleus of the nucleated erythrocyte precursors in the marrow. Finally, megaloblastic anemias, usually evident from examination of the peripheral smear, can be distinguished from nonmegaloblastic macrocytic anemias by marrow aspiration.

Bone marrow biopsy, which allows assessment of marrow architecture and cellularity, is useful in confirming the presence of myelophthisic, hypoplastic or aplastic states.

Therapy

In general, the physician should delay therapy for anemia pending the orderly evaluation detailed above and a diligent search for its underlying cause. The physician should admit those patients to hospital for observation, diagnostic evaluation and consideration of transfusion therapy (1) who are elderly, particularly those with angina pectoris, congestive heart failure or prior myocardial infarction, (2) who have severe degrees of anemia (hemoglobins below 7 grams per dl) or pancytopenia and (3) in whom anemia develops rapidly, especially those with acute hemorrhage. In such cases, the practitioner should rapidly carry out the basic laboratory studies (complete blood

count, smear, reticulocyte count) and set aside a sample of serum for further studies before the patient receives transfusions.

Finally, with the exception of short-term therapeutic trials of iron in a patient with microcytic-hypochromic anemia, or low-dose folate in a patient with macrocytic anemia, the physician should avoid the use of empiric therapy before achieving etiologic diagnosis.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Plasmapheresis

QUESTION:

Is plasmapheresis (plasma exchange) an accepted treatment for the following conditions: (1) severe myasthenia gravis, (2) refractory, severe progressive systemic sclerosis (scleroderma), (3) polymyositis, dermatomyositis and myositis, (4) Goodpasture's syndrome, (5) acute crescentic nephritis or (6) lupus nephritis?

OPINION:

It is the opinion of the Advisory Panels on Allergy, Dermatology, Internal Medicine and Neurology that plasmapheresis is an accepted treatment for severe myasthenia gravis. There have been reports of significant benefit; however, most patients have been placed simultaneously on regimens of immunosuppressive drugs and the available data do not indicate whether plasmapheresis alone, in the absence of such immunosuppression, can produce the same significant degree of improvement. This treatment should be reserved for patients in whom therapy has failed with anticholinesterase drugs and high-dose, alternate-day steroids and whose respiratory function is significantly compromised. It also would have a role in the preoperative management of a patient with severe involvement and respiratory compromise who is to undergo thymectomy.

Where conventional forms of therapy have failed, plasmapheresis is also an accepted treatment for certain types of nephritis and progressive renal insufficiency, such as Goodpasture's syndrome, acute crescentic nephritis and lupus nephritis. Such conditions should have rapid progression, multisystem involvement and at least postulated circulating immune complexes etiologically.

Plasmapheresis should be administered under a well-defined protocol on selected patients by physicians and nurses well experienced in acute patient care and extracorporeal circulation.

There are insufficient scientific data available to the Advisory Panels at this time to comment on refractory, severe progressive systemic sclerosis (scleroderma) or polymyositis, dermatomoyositis and myositis.

The Quality Care Review Commission acknowledges that plasmapheresis is a treatment modality whose efficiency is the subject of current medical investigation. The Commission will reconsider the above opinion as sufficient data become available.

Refer to: Haller JS Jr: The foul tongue: A 19th century index of disease (History of Medicine). West J Med 1982 Sep; 137:258-264

The Foul Tongue: A 19th Century Index of Disease

JOHN S. HALLER, Jr, PhD, *Long Beach, California*

I can speak but one language, but I can understand many tongues.

GEORGE DUFFIELD
Transactions, Michigan Medical Society, 1892

FROM THE DAYS of Hippocrates through the latter decades of the 19th century, symptomatology of the tongue was an important index in health and disease. Like the eyes, pulse, respiration, digestion, secretions, excretions, senses and facial countenance, the tongue provided one of the crucial signs for early diagnosis. Understood by many to be a mirror of the body, the tongue indicated conditions of the digestive organs, composition of the blood, the state of the secretions and even the condition of the nervous system. Indeed, for some physicians, an entire book of prognostics was written on the surface of the tongue. Its color, movement, degree of moisture and amount of fissuring, as well as the condition of the papillae, were all factors to take into account when attempting to comprehend the state of a patient's health.

Physicians who examined patients in the 18th and early 19th centuries asked to see the tongue as a matter of course. As a patient exposed the tongue for a few moments, its condition and characteristics were carefully examined along with other body signs. Disturbances that were known to produce changes in respiration, secretions and excretions were understood to be evident in the moisture of the tongue, the coating on its surface and the different shades of its color. The movements of the tongue signaled exhaustion, nervous disorders, paralysis and cerebral lesions, while the volume of the tongue indicated ailments of the digestive organs, affections of the brain, circulatory difficulties and distempers.[1]

Most advocates of examination of the tongue recognized that certain elements complicated quick assessment, including the fact that people were of different constitutions. Sanguine persons, for example, could not be expected to have the same natural coloring of the tongue as those who were lymphatic.[2] Another difficulty stemmed from the use of vague and often confused terms that prevented clear classification of changes or conditions of the tongue. Words such as "loaded," "furred," "coated" or "dirty" were used interchangeably by doctors to describe gross changes in appearance. Despite inconsistencies in terminology and complications related to constitution, the appearance of the broad, white-coated, pallid tongue or the deep red, sleek tongue or the pinched, shrunken, elongated, full, yellow-furred, violet or dark brown tongue was considered either indicative of specific diseases or symptomatic of diseases in different stages of virulence or remission.[3-5]

The schools of John Abernethy (1764 to 1831) and François J. V. Broussais (1772 to 1838) were especially supportive of tongue assessment, though they perhaps sometimes overrated its possibilities. Both men thought the tongue reflected exactly the morbid condition of the alimentary canal. Later medical writers like Williams,[6] who was a disciple of Pierre C. A. Louis (1787 to 1872), the father of the modern method of note taking and mathematical accuracy, stressed the importance of empirical evidence derived from observation, symptoms and generalizations based

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GLOSSOLOGY,

OR THE

ADDITIONAL MEANS OF DIAGNOSIS OF DISEASE

TO BE

DERIVED FROM INDICATIONS AND APPEARANCES OF

THE TONGUE.

A PAPER read before the Senior Physical Society of Guy's Hospital, 4th Nov. 1843,

BY BENJAMIN RIDGE, M.D., M.R.C.S.E.

"There is much truth in the statements of the author in justifying his attempt to establish a new doctrine, viz. that unless it be based upon facts, it will share the fate of many of its predecessors, and be speedily forgotten. The importance of diagnosis must be too evident to require additional comment; and in as far as this desideratum can be accomplished by external signs, every attempt to facilitate it is praiseworthy. The doctor takes a different view of the papillæ from that of most of his contemporaries. They are not, as generally supposed, the fine points of the gustatory nerves, devoted to the sense of taste, but they are follicles destined to the secretion of mucus. These are divided into different kinds. The advantages of the author's opinions upon the use of studying the appearances of the tongue, under certain guidance, are superior to any we hitherto enjoy, because they not only afford us a correct view of the system in general, but they put us '*above our patient*,' and enable us to detect any attempt at concealment or misrepresentation."—*The Lancet.*

"Dr. Benjamin Ridge's observations will, doubtless, prompt to a more attentive study of the diagnostic value of the tongue, (a study which cannot but prove of great service,) and are characterized by a disinterested earnestness of purpose, an ability and spirit of scientific research, which command the critic's respect, even when the author fails to win his assent."—*The Medical Times.*

"This treatise contains the substance of a Paper read by Dr. Benjamin Ridge, before the Senior Physical Society of Guy's Hospital; and certainly, should the truth of the doctrines propounded in it be confirmed, Dr. Ridge has made one of the most vitally important discoveries that has been made since the days of Hunter ..... Should Dr. Ridge's views prove correct, it is impossible to exaggerate the importance of the science of Glossology, not only in the diagnosis of disease, but as a means of detecting deception.

"This book is well worthy the careful attention of the medical profession. Every practising member of that profession has the power of investigating the truth of these doctrines: and it is a duty he owes to himself, to his profession, and to his fellow-creatures to do so; for the nearer the approach to certainty in diagnosis, the nearer the approach to certainty in the application of remedial agents."
The Sun.

N.B. This PAPER was published by the author merely as an Introductory Address to the study of the appearances of the tongue in disease, under certain rules. It is, therefore, intended only as a grammar or elementary part of a system to be hereafter more fully described, when cases and pathological appearances will be brought forward to illustrate the truth of the indications of the tongue in disease. It is also intended to form an introduction to a NEW THEORY of the Practice of Medicine. By the tongue indicating the state of the system, a classification of disease, therapeutics, and diet will be made. These classes will be shown to correspond with each other, so as to ensure the ready application of remedial agents to particular maladies.

PUTNEY, *April*, 1844.

JOHN CHURCHILL, PRINCES STREET, SOHO, LONDON.

Preparing for the press, by the same Author,

A DESCRIPTION OF A NEW MEMBRANE,

Lately discovered by Dr. BENJAMIN RIDGE, with its uses in the early ages of Animal Vitality. Also some contributions to the Physiology of the Fœtus and Placenta. With coloured Plates.

Figure 1.—Title page of Benjamin Ridge's 1843 paper on diagnosis based on observing the tongue.

on a statistical or numerical method. As senior physician to the Essex and Colchester Hospitals, Williams made extensive numerical summaries on gastric functional derangements, including the effects made on the filiform and tuberous papillae of the tongue. Physicians such as Wood[7] (1797 to 1879) and DaCosta[1] (1833 to 1900) preferred to believe that the tongue, by participating in all general derangements of the body, served as a guide to "the degree, prognosis, and precise stage of the disease," but did not necessarily discriminate one specific disease from another. The differences in these points of view precipitated substantial debate in 19th century diagnostics.[1,7]

The disciples of Abernethy and Broussais routinely examined the tongue as a means of clarifying the causes of specific diseased states. According to Ridge,[8] in a paper read before the Senior Physical Society of Guy's Hospital in 1843 (Figure 1), the areas of the tongue were guideposts to specific diseases; when properly understood, the effects of disease on these areas allowed doctors to diagnose with greater accuracy and prescribe remedies with more precision than ever before. His observations during an epidemic of influenza in 1836 and 1837 caused him to notice three distinct stages of the disease—affecting, in order, the stomach, lungs and brain—with each stage presenting distinct characteristics on the tongue. In keeping with these observations, Ridge divided the tongue longitudinally into three distinct parts: central laterals, or small portions on either side of the raphe; laterals, to the outer sides of the foregoing, and edges. He then divided each of these parts by means of transverse lines into anterior fourth, second fourth, central fourth and posterior fourth. Besides the longitudinal and transverse divisions, Ridge designated the tip, sides, cornua, root and oval as sections of the tongue providing additional means of diagnosis of disease.[8(p 19),9]

Ridge maintained that the tongue could point to the particular organ affected in all chylopoietic derangements, indicate the seat of disease in respiratory and circulatory complaints and act as a major guide in the diagnosis and treatment of fevers (see Figure 2). The central laterals, for example, corresponded to the respiratory organs (larynx, trachea, bronchi and lungs), whereas the laterals were apportioned to the chylopoietic viscera (pharynx, esophagus, stomach, duodenum, liver, spleen, pancreas and small intestine). The edges were guideposts to the brain, the tip indicated the state of the large intestines, the oval signified the state of the pleura and the whole of the tongue was an indicator for the heart.[8(pp 23-25)]

Thus, with the elongated and pointed tongue physicians could diagnose irritation and make a determination of blood to the stomach and intestines. When found in children, these signs prompted physicians to divert the blood from the stomach and bowels, being careful not to aggravate the constitution with an irritating cathartic. When the tongue increased in size and density, with the surface drier and whiter than in good health, and a "dirty-white fur" covering the entire dorsum and obliterating the papillae, physicians prepared for approaching inflammation arising from congestion of the capillaries and veins. A yellowish tongue was considered symptomatic of a disorder caused by the absorption of bile into the vascular system. Physicians were cautious, however, not to make a firm diagnosis in situations of this latter type until certain that a patient was not a tobacco or licorice chewer because chewers nearly always had yellow-coated tongues and healthy livers. The same admonition applied to the conditions of dryness and moisture; persons who slept with their mouths open were apt to have dry tongues.[10,11]

In cases where the tongue was relaxed, with diminished size and density and exhibiting a "pale hue" combined with a "dirty-white mucus fur," physicians suspected idiopathic fever and sometimes typhus. In measles the tongue was thickly coated, moist, with red papillae projecting through the thick coating of fur. Diphtheria presented a moist tongue with a thin "creamy fur," while a moist tongue that was covered with a "white creamy fur" but red at the tip and edges was a sign of influenza. In acute dysentery, the tongue was red at the edges and dry, then dark brown and sometimes even black. In diabetes the tongue was irritable, clean, cracked and red. And in scarlet fever the papillae were large and prominent, projecting through the fur so that the tongue presented a peculiar "strawberry" appearance.[10,12]

In addition to inspection of the surface, edges and color of the tongue, some physicians also recommended an examination of the lingual veins for signs of vascular change in the system. In elderly persons, the ranine and lingual veins were especially dilated and varicose and easily observable when a patient placed the tip of the tongue against the upper incisor teeth. Vascular changes in the encephalon were liable to occur when there

was evidence of a varicose state of the linguals. "The lingual vein being a branch of the internal jugular," wrote Dickson in 1885, it "will indicate the state of the blood-current in it, and so will approximate to the state of the brain-sinuses, the veins of Galen, and indeed, the whole intracranial venous system. Distension and varicosity of the linguals will become associated with passive congestion in them, precisely the conditions in which thrombotic and hemorrhagic lesions are apt to occur."[1] Although the capillaries of the nose, lips and ears gave similar clues to the state of circulation in the head, Dickson believed that the lingual vein was a much more precise indicator. He concluded that the condition of the linguals was of great diagnostic vaue, as careful obser-

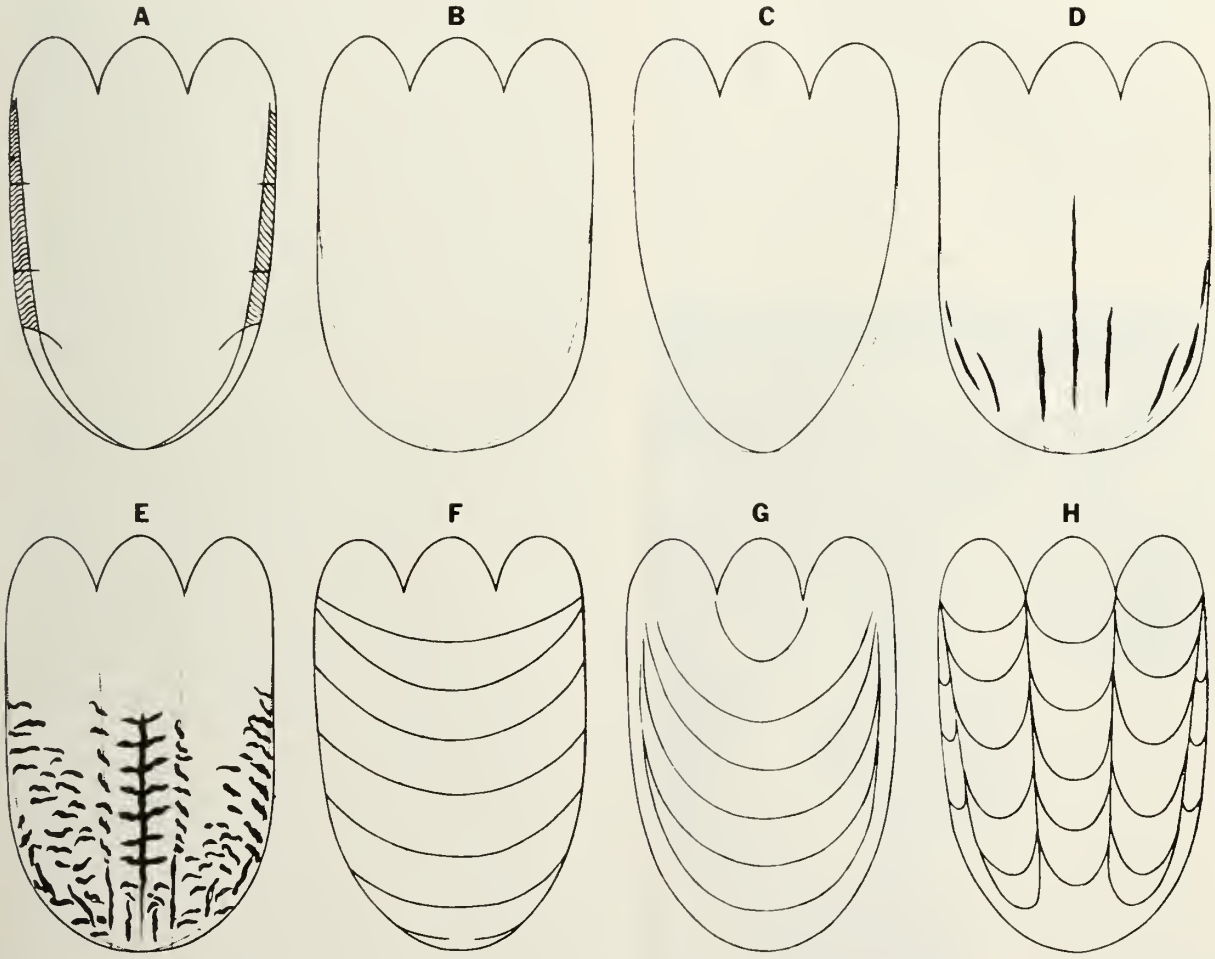

Figure 2.—Illustrations adapted from Benjamin Ridge's *Glossology, or the Additional Means of Diagnosis of Disease to be derived from Indications and Appearances of the Tongue*[5] (Courtesy of the National Library of Medicine).

A. The rugae, or serrated edges of the tongue occurring in congestion of the membranes of the brain, the effects of which are headaches, vertigo, etc.

B. The wide or rheumatic tongue. The dotted line shows the natural size of the organ.

C. The pointed tongue of fever and inflammation. The dotted line shows the natural size of the organ.

D. The longitudinally fissured tongue, indicating dilatation of the heart and effects of irregular circulation of the currents of the blood. The longitudinally dotted lines show the situation of these fissures: the circular dotted lines show the natural size of the organ.

E. The longitudinally and transversely chapped, fissured and sulcated tongue, indicating dilatation and hypertrophy of the heart and effects of irregular circulation of the currents of the blood. The longitudinal and circular dotted lines show the situation of these fissures: the circular dotted lines show also the natural size of the organ.

F. Laws of the fouling of the tongue, from the posterior to the anterior part, from edge to edge.

G. Laws of the cleaning of the tongue, from the anterior to the posterior part, in a more pointed cone shape than in fouling, and leaving the edges.

H. Laws of the cleaning of each apportionment of the tongue, viz. of the edges, the laterals and center laterals.

vation would give clues to the state of the entire jugular system.[13-15]

While many skeptics were reluctant to accept the excessive enthusiasm of Ridge and Dickson,[8,13] there were those who did acknowledge the possibility of determining the "state" or "condition" of disease by the tongue's appearance. Dickinson[16] (1832 to 1913) of Brighton, senior physician to St. George's Hospital, came closest to approximating laws for understanding the tongue when he suggested in 1888 that the tongue was really an index of constitutional states rather than of individual diseases. He dismissed the claims of Ridge who had insisted that the tongue presented "a map of the empire of disease," with each section of the tongue reflective of specific body organs or functions. The tongue, he argued, had no local significance and seldom, if ever, pointed to single organs or isolated disorders; rather, the character of the tongue was a "gauge of the effects of disease upon the system." The kind and character of disease required reference to other available signs.[16(p 730)]

Dickinson, who owed much of his research to the labors of Jonathan Hutchinson, surgeon to the London Hospital and professor of surgery at the Royal College of Surgeons, to Sweeting and Armstrong of the Western Fever Hospital and to Collie of the Eastern Fever Hospital, suggested the following categories as characteristic states of the tongue in disease.

Stippled or Dotted Tongue. This condition, known by its excessive coat or fur that, rather than uniformly spread across the tongue, was displayed only on the points of the papillae, signaled one of the early morbid changes occurring in disease.

Stippled and Coated Tongue. This condition, identifiable by a white accumulation on the papillae and a dotted character about the anterior and lateral parts, was common in chronic diseases and acute constitutional infections and was usually accompanied by increased pyrexia and prostration.

Coated Tongue. Marked by a continuous coat over the greater part of the dorsum, this tongue type was common in cases of pneumonia, pleurisy and typhoid when pyrexia and prostration were on the ascent. If the coated tongue thinned off "with a shelving edge," exposing a moist and natural surface, the prognosis was for the restoration of health. If the coating broke away in flakes, displaying a reddened and dry surface, the change was a sign "of more serious import."

Strawberry Tongue. This striking condition, commonly associated with acute febrile diseases such as pneumonia, typhoid and perityphlitis, was also a pathognomonic symptom of scarlet fever.

Plastered Tongue. This classification was considered a variety of the coated tongue and a sign of acute febrile disease, deficient saliva and prostration. It was also evidence of the seriousness of a patient's condition and a signal to an attending physician that a patient was not responding to treatment.

Furred or Shaggy Tongue. This condition, common among those suffering from a lack of nutrition and vital power, was identified when the papillae of the coated tongue continued to lengthen, giving the semblance of "a coarse pile-like plush." When the fur began to recede from the tip and edges of the tongue, doctors looked for rapid recovery. When it separated in flakes and patches, leaving a smooth, red, glossy surface, convalescence was apt to be more tedious; and if the fur withdrew, exposing a raw appearance or a fissured, dark colored tongue, the prognosis was most unfavorable.

Encrusted Dry and Brown Tongue. Characterized by a dry brown crust that was broken and fissured and that covered the tongue and concealed the papillae, this condition was a sign of protracted fever requiring immediate use of stimulants. It was so characteristic of typhus that physicians often referred to the condition as the "typhoid tongue." When accompanied by low fever, it was typical in cases of abdominal cancer, advanced phthisis, albuminuria, syphilitic mania, diarrhea, alcoholism and coma.

Bare, Red and Dry Tongue. This classification, along with the red, smooth and dry tongue, marked a later stage of the encrusted dry and brown tongue and implied failing nutrition, deficient saliva and, unless there was resumption of natural moisture, was judged to have an unfortunate prognosis. Of the 30 cases that Dickinson observed at St. George's Hospital, 16 ended in death.

Cyanosis or Venous Congestion of the Tongue. This type was characterized by a deep epithelium, a bluish or purple color and a smooth slippery surface and was common among patients suffering from heart disease.[16(pp 627-632, 677-680)]

Along with the pulse and thermometer, Dickinson considered these classifications significant indexes to the bodily constitution. Clinically, he wrote, the tongue always spoke the truth "and in a language which is not foreign to the experienced physician." Conditions of fever and nutrition, the

state of the nervous system and vital secretions and the failure of vitality were all apparent in the state of the tongue. Whether the disease was getting the better of the patient or the patient the better of the disease—both were discernible to the educated eye. "The clinical value of the tongue," he concluded, "largely depends on the number of interests it represents; those are more or less mingled in its indications, and the impression they convey is a combined one, but it is none the less valuable because . . . it gives to a glance what otherwise could only be learned by detailed inquiry."[16(p 730),17]

Not all doctors who wrote on diagnostic assessment of the tongue were as supportive as Dickinson and the disciples of Ridge. Hardin,[18] writing in *Langsdale's Lancet* in 1898, for example, was convinced that much of the "pretended knowledge of the tongue in the past has been an idle dream." While not wishing to deprecate the work of Dickinson, who had emphasized a thorough clinical approach, Hardin was convinced that most physicians who advocated the tongue as a diagnostic indicator did so without sufficient care or thoroughness. The age demanded skillful diagnostics, which meant the "power to differentiate between a coating of the tongue produced by sleeping with an open mouth, and one produced by severe illness." As far as Hardin was concerned, not all those who drew their medical wisdom from the tongue were that discerning. He concluded that if practitioners relied on the tongue as a guide to clinical diagnosis then it had not served this purpose; if viewed as "an outer index to changes beyond their sight," the tongue had not been used with much accuracy by those who advocated its use the most.

Clearly, Hardin admitted, the tongue "stands at the gateway of the alimentary tract, and by continuity of structure to the tissues below, causes it to partake, to a degree at least, of many of the morbid processes" affecting those organs. Nevertheless, doctors would gain greater knowledge of disease if they pursued the study of the nervous system rather than the tongue. The nervous system was the "presiding officer" of heat formation, heat regulation, distribution, elimination and glandular secretion. That system, rather than the tongue, was the key to more accurate diagnosis and prognosis. When doctors learned how to assess the nervous system, and especially when they learned how to regulate it through appropriate pharmacotherapeutics, medical science would have advanced further toward an understanding of health and disease than through any like effort to understand the varieties of tongues.[18]

Although practitioners in the early years of the 20th century chose to rely more heavily on instrumentation, semeiology of the tongue was not without its advocates (see Figure 3). For Christenbery,[19] writing in the *Journal of the Tennessee Medical Association* in 1911, the tongue remained an important index to the body's internal workings, especially the intestinal tract. Jones[20] of Buffalo was also a confirmed believer in the diagnostic attributes of the tongue. Whereas some doctors thought it necessary to examine the urine and feces to determine whether patients were digesting their food, Jones relied on his observation of the tongue that "would tell him at once the condition of the patient's stomach." A thick pasty-white or

Figure 3.—An Argentine pharmaceutical poster (c. 1920) shows a physician examining a young woman's tongue. Above the title the text asks if the patient's tongue is coated, in which case she would be a possible candidate for Reuter's Pills. (Exhibited in 1981 in a show commemorating the 100th anniversary of New York's Albany College of Pharmacy, the poster is from the private collection of William H. Helfand.)

dirty-white coating was a signal that the system was in need of alkaline salts, a broad pallid tongue with a white pasty coating called for bicarbonate of soda and a deep red mucous membrane and brown coating was a sign that the system was in need of acids. "When we know how to read the eye, pulse and tongue of a patient intelligently," Jones concluded, "it is ten times as easy to prescribe for the sick, and it enables a doctor to get right at the real condition of a sick person."[20]

In part, those physicians in the early 20th century who advocated a greater use of the tongue in diagnosis did so from a concern that medical practice had fallen on evil times. As one physician explained it, "a wave of therapeutic pessimism" had settled on medicine as physicians felt less sure of their own accuracy of observation and ability to reason correctly. Choosing to rely almost entirely on laboratory tests and instrumentation, physicians appeared to have forfeited sound judgment and the evidence that a keen clinical eye could discern.[21-23]

This reasoning notwithstanding, semeiology of the tongue remained in the backwaters of 20th century medical practice. Although an aid in diagnosis, it was of inconsistent value, as many physicians readily admitted. Shackelford[24] remarked that the color and texture of the tongue were "helpful confirmatory evidence" in some gastrointestinal disturbances. Nevertheless, there were simply too many causes for a discoloration of the tongue—from drugs, dyes and hemorrhage, to jaundice, tobacco, blueberries and scarlet fever. It was just too difficult to separate the various conditions of the tongue with any degree of precision to allow for exact diagnosis, treatment and prognosis.

Although semeiology of the tongue was, in some of its aspects, almost as old as medicine itself, in other respects it dates with the stethoscope and thermometer; only in the 19th century did the condition of the tongue become the subject of extensive clinical research. The knowledge that physicians drew upon to make the tongue an index in the diagnosis, treatment and prognosis of disease was, however, for the most part unwritten and loosely explained. Conclusions drawn from its signs were often little more than mischievous dogmatisms built on precarious revelations having little basis in fact. While vast experiences had accumulated over the ages to contribute to the wisdom of physicans, those few attempts made to analyze or otherwise deduce laws on semeiology of the tongue were too little and too late.

Overall, physicians preferred the stethoscope, ophthalmoscope, sphygmograph, thermometer and tests of urine and blood in clarifying diagnosis, treatment and prognosis. Those few who continued to advocate diagnostic assessment by use of the tongue admitted that the condition of the tongue could not be considered a primary index to the pathologic condition of any particular organ, though changes in it could be viewed as an indicator to the degree of seriousness in a given illness. By itself, however, the tongue was an inappropriate source of diagnosis or even prognosis; only in connection with other signs, and recognizing that the tongue was subject to varied modifications independent of disease, could a physician rightfully consider its significance—both clinical and pathologic.

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Information

Treatment of Impaired Physicians/The California Board of Medical Quality Assurance Program

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Professional impairment is not a rarity and the hazards for health professions can be many. The California Board of Medical Quality Assurance has instituted a treatment and rehabilitation program for impaired physicians in which, at the completion of the program, a treated physician's records are purged. Although it is too early to evaluate the effectiveness of the program, preliminary data have been useful in pointing out the types of impairment that are being seen. Impaired physicians tend to have a higher than normal incidence of substance (tranquilizers, sedatives and stimulants) abuse, to be young (about 44 years) and to have had barren childhoods. Women physicians may be especially vulnerable to the stresses of the profession.

THE PREEMINENT RESOURCE of any society is its people. In the United States a significant and increasing portion of the gross national product is expended on maintaining the health of this resource. In a highly technologic environment, the stresses on each person to adapt to a rapidly changing milieu are considerable. The health care system then becomes the container for many who cannot adapt or, more frequently, who maladapt to their life circumstances and have physical or mental disorders (or both). What happens, though, when healers themselves become impaired?

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ABBREVIATIONS USED IN TEXT

BMQA = Board of Medical Quality Assurance
DEC = Diversion Evaluation Committee
DMQ = Division of Medical Quality

Impaired Physicians

The American Medical Association Council on Mental Health published a report, "The Sick Physician," in 1973[1] that dealt with the importance of recognizing professional impairment and of assisting a disabled physician in obtaining appropriate treatment. The depth of the problem was underscored by a rate of 125 disciplinary cases per year in California alone at that time; most of these cases involved the use of narcotics. Recommendations included a stepwise program of assisting impaired physicians into treatment, progressing from approaching a person with evidence of impairment by colleagues, hospital staff, medical society committees on well-being and, finally, the state licensing board.

A seven-year study at the Mayo Clinic involving psychiatric hospital admissions of 93 physicians found the mean age of those presenting for treatment to be 54 years old, with 73 percent having no previous psychiatric history and 63 percent being admitted to a closed unit.[2] A wide spectrum of psychiatric diagnoses was found, with a low incidence of organic brain syndrome and a high incidence of drug and alcohol abuse. In interviews with 98 recovered alcoholic physicians abstinent for a minimum of a year, self-reports of academic achievement identified these persons as doing remarkably well through medical school.[3] Often it is several years after the completion of training that habitual substance abuse develops. Approximately half those interviewed had abused other drugs in addition to alcohol.

Vaillant and co-workers[4] did a 20-year longitudinal study of 45 physicians and 90 controls addressing the use of psychoactive drugs. All of the subjects had been selected during their undergraduate years for indices of physical and mental health. The use of tranquilizers, sedatives and stimulants was greater among physicians than

controls, though both groups equally used alcohol and cigarettes. In addressing the physician as patient, the authors warned that the "patient's tendency to deny illness will make a diagnosis difficult; secondly, the patient's virtue of not troubling his doctor may lead to the wish to self-prescribe; and thirdly, the patient's willingness to care selflessly for others may conceal a greater than average need to be given to." A person's use of denial, reticence to seek treatment and underlying unmet psychologic needs must then be considered when addressing the problem of impaired physicians.

Characteristics of Impaired Physicians

The defenses used by disabled physicians frequently include denial, avoidance and rationalization. Retrospective accounts have found substantial familial difficulties in the childhood and adolescence of these physicians that may be a prime mover in their motivation to enter the helping professions. In a further report of the long-term study mentioned above, Vaillant and colleagues[5] noted that physicians, especially those in primary care specialties, tended to have more marital maladjustments, abuse of substances and use of psychotherapy than controls. Physicians most vulnerable to becoming impaired have been seen as those having a barren childhood and surrounding themselves with needy patients. Overwork per se was not found to lead to impairment, though commonly cited by disabled physicians as the reason for their difficulties. Possibly the stress of giving to patients who tend to be dependent by those who themselves have histories of unmet nurturant needs predisposes to professional dissatisfaction and ill-being. These personality traits are based on psychoanalytic theory, however, and have not been shown definitively to be causative factors.

A 15-year study of 65 patients treated for narcotics addiction at the Menninger Institute involved 30 physician addicts.[6] Data at time of admission on the 25 physicians who continued in the study group showed the mean age to be 41 years old, the average length of addiction to be three years and that most physicians had been admitted to hospital for addiction at least twice previously. This group is younger and with a significantly higher previous use of psychiatric services than those in the Mayo Clinic study.[2]

Where Vaillant and associates describe the typical impaired physician's childhood as barren, Modlin and Montes[6] reported a common finding of sickness in the early years. The physicians were often studious and ambitious throughout adolescence. Parents were often seen as unavailable. Fathers were described as stern and depriving, passive and indifferent, volatile and flamboyant or irritable and withdrawn and most fathers had problems with alcohol abuse. Mothers were seen as nervous, pushy, demanding, dominating, depressive, perfectionistic, harsh, distant, protective or alcoholic. Hence, the family backgrounds that impaired physicians develop in are perceived by them as lacking in warmth and caring. It then may come as little surprise to find that these persons have difficulties with their spouses, lack interest in child-rearing and have a 75 percent incidence of sexual dysfunction.

Physicians themselves report overwork, fatigue and disease as precipitants for their use of drugs and alcohol. The authors, however, postulate that unmet professional expectations lead to disillusionment and regression. Psychiatric disability develops later in these professionals than in many other addicted and alcoholic patients. A possible explanation for this is that the structured environments of medical school, internship, residency and entry into practice become alternative family settings that allow the attainment of adulthood to be postponed. On being confronted with the reality of being independent and not magically provided for by the profession, these physicians retreat to more primitive oral-dependency gratification.

A subsequent study of drug- and alcohol-addicted doctors (43 with MD degrees and 7 dentists) at the Menninger Memorial Hospital showed a mean age in the study population of 46.5 years, with 76 percent practicing medicine till the time of admission.[7] Diagnostically, those under 40 years of age were felt to have more serious psychopathology, often of a severe characterologic sort, whereas those over 40 had a greater incidence of organic brain syndrome and depression. Again, the use of denial, both in the need for admission to hospital and possible impairment in treating patients, was observed.

Female physicians may be especially vulnerable to the stresses of the profession.[8] Of 751 deaths of women physicians over a five-year period (1967 to 1972), 49 were due to suicide, with an annual rate of 40.7 per 100,000 population. This is higher than the suicide rate for male physicians and four times that for nonphysician women

matched for race and age. Though Stevens and Shore[9] disagree with the study's extrapolation of the 65 percent prevalence of affective disorder in female physicians, the high suicide rate is a finding not easily dismissed. A comparison of women health professionals found fourfold the amount of affective disorder in physicians compared with psychologists.[10] The reluctance to seek professional help is revealed by a fifth of the depressed physicians having treated themselves with antidepressant medication. In both populations, depressed persons tended to report more job discrimination than nondepressed professionals, and women with children experienced more career disruption. There may be some common stresses that health providers are subject to and respond similarly to, yet physicians may be more at risk than other helping professionals.

Colleagues' Attitudes Toward Impaired Physicians

Aside from a physician's family, peers may be the first to recognize a deterioration in clinical skills and means of interacting with others. Physicians should be most aware of indications of mental or physical ill-being, however subtle. Yet, the denial that an impaired person functions under can operate for colleagues who identify with the compromised physician. Duffy and Litin[2] noted behavior among impaired physicians' colleagues that included a reluctance to intervene, a propensity to overprotect and a stance of rejection toward disabled physicians. Chappel[11] has more recently addressed physicians' attitudes toward professional impairment. He identifies negative responses as silence, avoidance and permission versus the more positive responses of confrontation, assistance into treatment and education regarding the risks of the profession. Recommendations were made for the development of confrontational skills in all physicians and the involvement of paraprofessionals and formerly impaired physicians in a disabled physician's care.

Certain state legislators have recognized the extent of the problem of physician impairment and have enacted laws to assist in the recommendations that investigators such as Chappel have made. Talbott and co-workers[12] have reported on the disabled doctors' plan in Georgia, which has been in operation since 1975. The Medical Association of Georgia, in cooperation with the state board of licensure, developed a program with clear treatment objectives and well-delineated phases of treatment (that is, residential care, outpatient services, physician's apprenticeship and reinstitution of professional activities). After 18 months of operation, the Georgia program had assisted in returning 62 percent of those entering treatment back to their professional positions.[12] Bloom[13] emphasizes the ubiquitous nature of the impaired physician syndrome and mentioned the Johnson Institute of Minnesota model of intervention used by the California Medical Association. The California situation is one testing

TABLE 1.—*Status of Referrals to the Diversion Program for Physicians (February 1980-March 1, 1981)**

Status	*Program Referrals* *number*	*(percent)*
Active (n=80)		
Seeking admission or participating in the diversion program		
Participants in program and in treatment	52	(47.3)
Potential participants accepted by the Diversion Evaluation Committees and awaiting treatment programs	13	(11.8)
Awaiting evaluation before a Diversion Evaluation Committee	15	(13.6)
Inactive (n=30)		
Terminated from diversion program participation	1	(0.9)
Referrals not resulting in diversion program admission		
Accepted by the Diversion Evaluation Committee but became ineligible before initiating treatment	2	(1.8)
Determined by the Diversion Evaluation Committee to be unacceptable for the program	3	(2.8)
Lack of interest in entering program	15	(13.6)
Ineligible/did not meet entry criteria	9	(8.2)
TOTAL REFFERALS	110	(100.0)

*From the report of the diversion program for physicians, State of California Board of Medical Quality Assurance, 1981.

TABLE 2.—*Types of Disorders in Physicians in Active Status in California Diversion Program**

Disorder	*Men*	*Women*	*No. of Physicians*	*Mean Age*
Alcohol abuse	18	0	18	47.1
Drug abuse	28	3	31	39.1
Alcohol and drug abuse	12	1	13	44.2
Mental illness	5	1	6	47.3
Mental illness and substance abuse	8	1	9	48.3
Physical illness	1	0	1	52.0
Physical illness and substance abuse	2	0	2	55.0
TOTAL	74	6	80	43.9

*From the report of the diversion program for physicians, State of California Board of Medical Quality Assurance, 1981.

ground for treatment of this group of professionals.

California Diversion Program for Physicians

In California, with more than 50,000 doctors, a diversion program was instituted for physicians in January 1980 to address the problem of physician impairment. In the previous year the state legislature had directed the state's Board of Medical Quality Assurance (BMQA) to establish means for the identification and treatment of impaired physicians. The goal of the program is to rehabilitate those doctors with dysfunctions attributable to alcohol or drug abuse, mental dysfunction or physical illness that interfere with competence in treating patients.

Application for the program is reviewed by one of five Diversion Evaluation Committees (DEC) consisting of five experts in the treatment of mental illness, drug abuse and alcoholism. If accepted in the program, a person is asked to adhere to a written treatment contract that varies in each case. While in the program, there is no disciplinary action by the Division of Medical Quality (DMQ) of the BMQA regarding licensure. A DEC member is designated as case consultant and a compliance officer is assigned to check alcohol and drug use. Review of cases is made by the DEC. At the end of the rehabilitation period, envisioned as three to five years, the DEC then determines whether unsupervised practice can be reinstituted. If so, a treated physician's records are purged. Initial unacceptability or noncompliance at any point can result in a person's case being dropped from the program.

First Year of Operation

In its first 13 months of existence, 110 physicians have been referred to the diversion program, 80 were on active status with 52 in treatment as of March 1981 (see Table 1). Of the total population, 68 were referred either by the BMQA or the office of the Attorney General; 17 more had DMQ investigations in progress and 25 were self-referrals. The need for an external impetus into treatment is apparent and has been noted previously by those who treat disabled physicians.[7]

Of the 80 physicians who have presented for treatment, 74 were men and 6 women. Drug and alcohol abuse are present in most of the program population, with seven persons having mental or physical illness or both, without evidence of substance abuse. The drug abuse category of disability involved the largest number of physicians and had a mean age of 39.1 years, compared with the mean of the total of 43.9 years (see Table 2). In all diagnostic categories 52 physicians used drugs and the three most popular substances were meperidine hydrochloride (Demerol) (23), cocaine (15) and amphetamines (10). Other substances frequently used included pentazocine hydrochloride (Talwin) (9), diazepam (Valium) (8), marijuana (7) and Percodan (a combination of oxycodone hydrochloride and terephthalate, aspirin, phenacetin and caffeine) (7). Physicians have been noted in clinical reports over the last two decades to preferentially use narcotics, stimulants and tranquilizers. This pattern seems to hold today with the continued use of drugs such as meperidine; the additional use of cocaine and marijuana can be attributed to the change in our society's drug use pattern. Diazepam abuse is representative of newer medications with widespread use and abuse potential.

Conclusions

In its first year of operation, the diversion program has received more referrals than expected. It is too early to know the long-term results of the program, though elsewhere a 64 percent abstinence rate has been reported in addicted physicians 9 months to 4½ years following treatment.[7] These preliminary data point to the types of impairment seen in one professional group today. As more physicians enter "diversion," are treated and follow-up data become available, the results of the program can be assessed. A system

that uses public regulatory powers and peer pressure to bring impaired physicians into treatment may well be the most effective force in rehabilitation versus punishment.

As evidenced by the mean age of the physicians on active status in the program, an impaired physician can be seen as a resource with many potential years of service to society remaining following treatment. The rewards and gratification for physicians brought to treatment, their families, the health providers involved in caring for physicians seeking diversions and those patients treated by rehabilitated professionals warrant the continuation of the California Diversion Program. It is hoped that diversion will prove to be efficacious and become a model for assistance to impaired professionals.

Finally, questions that remain unanswered regarding the diversion program's effectiveness include what becomes of those physicians who apply and are considered unacceptable by the DEC, have a lack of interest in entering the program or do not meet entry criteria. Of interest to evaluation and redesign of the program would be the reasons that 15 applicants did not enter owing to "lack of interest." A delicate balance no doubt must be struck in meeting the needs of individual physicians versus those of the program as an organization. Here, too, the issue of coercive as opposed to voluntary treatment leads to the use of confrontative techniques with persons, who retain the option of not entering treatment.

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Information

Diabetic Retinopathy

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DIABETIC RETINOPATHY is one of the most feared complications of diabetes mellitus. The fear is justifiable, since diabetic retinopathy is the leading cause of new blindness in adults, and 84 percent of blind diabetic persons are blind due to diabetic retinopathy (see Table 1).

Retinopathy is divided into nonproliferative (sometimes called *background*) and proliferative varieties. Background retinopathy consists of hemorrhages, microaneurysms, hard exudates, cotton wool spots and macular edema. It is found more often in maturity-onset diabetes. Proliferative changes, seen more often in juvenile-onset diabetes, include flat and elevated neovascularization, both on and away from the optic disc. Neovascularization causes recurrent vitreal hemorrhages and sometimes retinal detachment.

The frequency of retinopathy is related more closely to duration of diabetes than to any other single factor, and approaches a 90 percent incidence after 25 years of diabetes. The relationship between metabolic control and retinopathy is somewhat speculative, however; Kohner's data[1] and Engerman's work[2] in Alloxan-diabetic dogs suggest that "good control," especially in the first five years after diagnosis of diabetes, can delay the onset of retinopathy for several years. After retinopathy is present, control to euglycemia may be of some benefit in retarding the progression. It is a clinical fact that severe retinopathy is observed not infrequently in patients alleged to have been in "good control" all their lives, and likewise the converse.

Current therapy, apart from whatever role might be played by careful medical management,

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TABLE 1.—*Facts About Diabetic Retinopathy*

1. Diabetes mellitus causes 12 percent of all cases of blindness in the United States.
2. 84 percent of blind diabetic persons are blind due to diabetic retinopathy.
3. If diabetes is diagnosed before age 30 (juvenile):
   - 5 to 10 years later 10 percent will have retinopathy,
   - 15 years later 50 percent will have retinopathy,
   - 25 years later 90 percent will have retinopathy.
4. If diabetes is diagnosed after age 40 (maturity):
   - 10 years later 50 percent will have retinopathy,
   - 20 years later 80 percent will have retinopathy.
5. In proliferative diabetic retinopathy (without treatment):
   - 50 percent of eyes with disc neovascularization are legally blind (less than 20/200) in two to three years;
   - 50 percent of eyes with other neovascularization are legally blind in five years;
   - After one vitreous hemorrhage, 33 percent of patients are legally blind in both eyes in one year, 33 percent are economically blind (20/60 to 20/200 in best eye) and 33 percent have 20/40 or better in best eye.

is limited to photocoagulation and vitreous surgical procedures. Both xenon arc and argon laser treatments have been used with good results to improve vision through reduction of macular edema in *nonproliferative* retinopathy. Indications for treating diabetic macular edema include 20/40 or worse vision, 20/30 or worse vision with *cystoid* macular edema or hard exudates encroaching on the center of the fovea. Photocoagulation is designed to obliterate completely all microaneurysms and intraretinal microvascular abnormalities that contribute to macular edema, as seen on fluorescein angiograms. The possible merits of photocoagulation in proliferative retinopathy have been evaluated in a randomized prospective clinical trial at 15 university diabetic eye centers under the sponsorship of the National Eye Institute.[3] Long-term benefits have been documented in more than two thirds of all patients treated by the laser photocoagulation technique. Pituitary ablation, once a popular therapeutic modality for diabetic retinopathy, has very few advocates today.

Vitrectomy is now available for patients with vitreal hemorrhages that fail to reabsorb within six months. This technique removes blood from inside the globe through a small incision in the pars plana of the ciliary body. Documented results with this new therapeutic modality show a 60 percent to 70 percent chance of improvement in visual acuity in the diabetic eye. Complications of vitreous operations include iatrogenic retinal holes and neovascular glaucoma secondary to rubeosis iridis.

Physicians are encouraged to insist that juvenile-onset diabetic patients, especially with a duration of disease of five years or more, have annual examinations by an ophthalmologist competent to evaluate diabetic retinas. Because several proliferative changes can occur in the absence of visual disturbance (for example, if there has been no vitreous hemorrhage or if the macula is not involved), one cannot rely on normal vision to indicate absence of retinopathy. Persons with maturity-onset diabetes should have annual eye examinations by an ophthalmologist competent to evaluate diabetic retinas to detect the presence of lipid deposits (hard exudates) or macular edema before vision is affected irreversibly. An eye consultation is indicated for any diabetic patient with any visual symptoms.

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in memoriam

California Medical Association

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Renger, J. John, Ventura. Died October 10, 1981, in Ventura of heart disease, aged 78. Graduate of Hahnemann Medical College of Philadelphia, 1938. Licensed in California in 1938. Dr. Renger was a retired member of the Ventura County Medical Society.

Stirrett, Robert L., Arcadia. Died January 28, 1982, aged 65. Graduate of the University of Toronto Faculty of Medicine, 1940. Licensed in California in 1946. Dr. Stirrett was a member of the Los Angeles County Medical Association.

Whitson, Robert O., Sacramento. Died January 27, 1982, aged 63, Graduate of the University of Texas School of Medicine, Galveston, 1942. Licensed in California in 1969. Dr. Whitson was a member of the Sacramento-El Dorado Medical Society.

Zwerling, Henry B., Oakland. Died January 15, 1982, aged 70. Graduate of Columbia University College of Physicians & Surgeons, New York, 1934. Licensed in California in 1942. Dr. Zwerling was a retired member of the Alameda-Contra Costa Medical Association.

Utah State Medical Association

Crockett, Kenneth Adams, Salt Lake City. Died April 6, 1982, in Salt Lake City, aged 70. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in Utah in 1940. Dr. Crockett was a member of the Salt Lake County Medical Society.

Reichmann, Wilford J., St. George. Died June 8, 1982, in Salt Lake City, aged 83. Graduate of the University of Cincinnati College of Medicine, 1926. Licensed in Utah in 1926. Dr. Reichmann was a member of the Washington County Medical Society.

Winget, Frank J., Salt Lake City. Died March 30, 1982, in Salt Lake City, aged 78. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in Utah in 1934. Dr. Winget was a member of the Salt Lake County Medical Society.

Washington State Medical Association

Bailey, Richard J., Scottsdale, Arizona. Died August 13, 1981, aged 81. Graduate of the University of Minnesota Medical School, Minneapolis, 1927. Licensed in Washington in 1938. Dr. Bailey was a retired member of the Spokane County Medical Society.

Gorton, Samuel H., Woodland. Died April 29, 1982, aged 59. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1946. Licensed in Washington in 1947. Dr. Gorton was a retired member of the Cowlitz Wahkiakum County Medical Society.

Hildebrand, Carl H., Seattle. Died June 13, 1982, in Seattle, aged 65. Graduate of the University of Nebraska College of Medicine, Omaha, 1942. Licensed in Washington in 1950. Dr. Hildebrand was a member of the King County Medical Society.

Hill, Robert M., Ellensburg. Died March 3, 1982, in Ellensburg, aged 68. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in Washington in 1943. Dr. Hill was a member of the Kittitas County Medical Society.

Judy, Harriet E., Spokane. Died September 11, 1981, aged 77. Graduate of the University of Oregon Medical School, Portland, 1933. Licensed in Washington in 1936. Dr. Judy was a retired member of the Spokane County Medical Society.

Kindschi, Jean Douglas, Spokane. Died December 24, 1981, aged 78. Graduate of the University of Wisconsin Medical School, Madison, 1932. Licensed in Washington in 1936. Dr. Kindschi was a retired member of the Spokane County Medical Society.

Kohl, Gerald C., Tacoma. Died January 17, 1981, aged 78. Graduate of the University of Iowa College of Medicine, Iowa City, 1928. Licensed in Washington in 1929. Dr. Kohl was a retired member of the Pierce County Medical Society.

Lee, Jack W., Tacoma. Died March 13, 1981, aged 66. Graduate of thte Creighton University School of Medicine, Omaha, 1950. Licensed in Washington in 1951. Dr. Lee was a member of the Pierce County Medical Society.

Mattes, J. Joseph, Bellevue. Died April 29, 1982, aged 79. Graduate of Hahnemann Medical College, Philadelphia, 1934. Licensed in Washington in 1939. Dr. Mattes was a retired member of the King County Medical Society.

Pelley, John W., Puyallup. Died November 12, 1981, aged 47. Graduate of the University of Minnesota Medical School, Minneapolis, 1961. Licensed in Washington in 1962. Dr. Pelley was a member of the Pierce County Medical Society.

Pinto, Sherman S., Tacoma. Died April 21, 1982, aged 76. Graduate of the University of Nebraska College of Medicine, Omaha, 1932. Licensed in Washington in 1946. Dr. Pinto was a member of the Pierce County Medical Society.

Reberger, Charles C., Tacoma. Died February 9, 1982, aged 57. Graduate of the University of Oregon Medical School, Portland, 1949. Licensed in Washington in 1950. Dr. Reberger was a member of the Pierce County Medical Society.

Rowberg, Raymond G., Spokane. Died October 23, 1981, aged 59. Graduate of the University of Minnesota Medical School, Minneapolis, 1946. Licensed in Washington in 1955. Dr. Rowberg was a retired member of the Spokane County Medical Society.

Struse, William P., Selah. Died December 21, 1981, in Selah of leukemia, aged 36. Graduate of Philadelphia College of Osteopathic Medicine, 1971. Licensed in Washington in 1975. Dr. Struse was a member of the Yakima County Medical Society.

Suzuki, M. Paul, Seattle. Died June 1, 1982, aged 78. Graduate of the Creighton University School of Medicine, Omaha, 1936. Licensed in Washington in 1938. Dr. Suzuki was a retired member of the King County Medical Society.

Willard, Don G., Tacoma. Died April 10, 1981, aged 70. Graduate of Northwestern University Medical School, Chicago, 1936. Licensed in Washington in 1936. Dr. Willard was a retired member of the Pierce County Medical Society.

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GENERAL INTERNAL MEDICINE SPECIALIST needed by 36-member multi-specialty group. Excellent practice opportunity; benefits and retirement program; all practice costs paid; early shareholder status. Prefer recent residency trained physicians only. Reply: Mr. D. R. Molesworth, Administrator, or Dr. Daniel Small, 1235 Osos Street, San Luis Obispo, California 93401.

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GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. Call us collect at (714) 997-0853, or send CV to Physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

CALIFORNIA: Free standing Urgent Care Center near Los Angeles. Established physician-owned center seeking career oriented physician with at least two years experience or ED residency, and management skills. Outstanding area for family living. Excellent remuneration + bonus plan. Send CV to: Eugene Keller, MD, 310 N. San Vicente, Suite 204, Los Angeles, CA 90048. (213) 854-3448.

FAMILY PRACTICE FACULTY POSITION. The Wyoming Family Practice Program at Casper invites applications for the position of Assistant Professor with the University of Wyoming. Opportunities for creative and innovative participation in the residency program as well as for professional growth and a reasonable family life. Requirements include board certification, willingness to do obstetrics, and preferably three to five years' practice and/or teaching experience. Excellent resources, salary, and fringe benefits. Contact Dr. Charles Huff, Director of the University of Wyoming Family Practice Residency Program at Casper, Wyoming. 1 (307) 266-3076.

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(Continued on Page 40)

REGIONAL MEDICAL DIRECTOR

The rapidly developing Health Force Medical Group is looking for a physician to manage two multi specialty medical groups in Bakersfield & Lancaster.

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The Service center, whch serves the health care community of the greater Seattle area, offers clients a range of support services including all aspects of specimen pick-up and transport; generation and timely delivery of result reports; specimen container supply deliveries; marketing support and local representation; and client relations service—including inquiries regarding the status of specimen assays and information on laboratory services and specimen processing needs.

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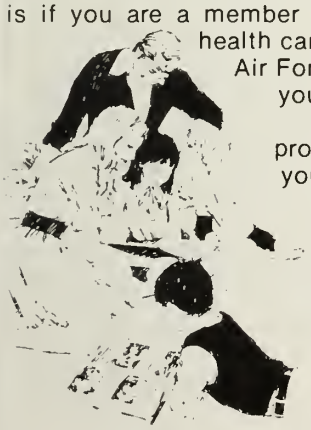

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(Continued from Page 38)

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PHYSICIANS WANTED

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CALIFORNIA TRAINED INTERNIST—Anxious to return to the Southern West Coast. Currently assistant professor at top midwest university. Box 6297, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 50)

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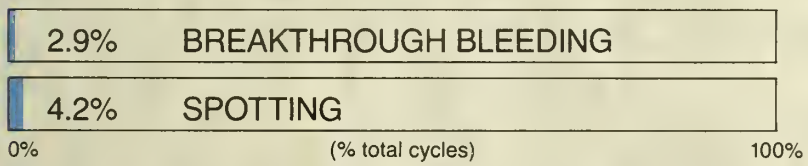

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3. Cerebral-vascular or coronary-artery disease.
4. Known or suspected carcinoma of the breast
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6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5). 8. Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group. Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g., thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.

A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users.

If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, ampicillin and tetracycline.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist, breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

Wyeth Laboratories, Phila., Pa. 19101

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see PROCARDIA® prescribing informa-
next page.

I. SCIENTIFIC PRESENTATIONS

Calcium Channel Blockers: Closing the Gap in Conventional Therapy of Angina
Harry E. Mayhew, M.D., F.A.A.F.P. **Moderator**
Professor and Chairman of Family Medicine
Medical College of Ohio

A Family Physician's Experience With Procardia®
J.S. Bailey, L.R.C.P., M.R.C.S., M.R.C.G.P.
General Practitioner
Oldham, England

Procardia® in Patients With Various Types of Angina Pectoris Refractory to Conventional Therapy
Peter Stone, M.D., F.A.C.C.
Associate Director
Levine Cardiac Unit
Instructor in Medicine
Harvard Medical School
Brigham and Women's Hospital

Procardia® in Unstable Angina Complicating Myocardial Infarction
Gary Gerstenblith, M.D., F.A.C.C.
Assistant Professor of Medicine
Johns Hopkins School of Medicine
Johns Hopkins Hospital

Worldwide Experience With Procardia®: Efficacy and Safety Versus Conventional Agents and Other Calcium Channel Blockers
Richard W. Terry, M.D., F.A.C.C.
Assistant Clinical Professor
University of California, San Francisco
Staff Cardiologist
Samuel Merritt Hospital

II. PANEL DISCUSSION

Panelists:

James Blackman, M.D.
Duluth Family Practice Center
Duluth, Minnesota

Harrison M. McCondless, M.D., F.A.A.F.P.
Santa Monica Hospital
Redondo Beach, California

Allan H. Bruckheim, M.D., F.A.A.F.P.
St. Mary's Hospital
Hoboken, New Jersey

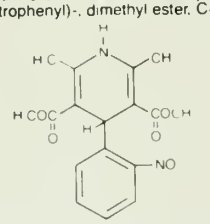
Through a new interactive electronic technique, the audience will be able to express their opinion regarding the management of angina pectoris. The cumulative audience response will then be discussed by the symposium participants.

Prescribing Information

PROCARDIA® CAPSULES (nifedipine)

For Oral Use

DESCRIPTION: PROCARDIA (nifedipine) is an antianginal drug belonging to a new class of pharmacological agents, the calcium channel blockers. Nifedipine is 3,5-pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, $C_{17}H_{18}N_2O_6$, and has the structural formula:



Nifedipine is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. It has a molecular weight of 346.3. PROCARDIA CAPSULES are formulated as soft gelatin capsules for oral administration each containing 10 mg nifedipine.

CLINICAL PHARMACOLOGY: PROCARDIA (nifedipine) is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. PROCARDIA selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without changing serum calcium concentrations.

Mechanism of Action: The precise means by which this inhibition relieves angina has not been fully determined, but includes at least the following two mechanisms:

1) Relaxation and prevention of coronary artery spasm: PROCARDIA dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of PROCARDIA in vasospastic (Prinzmetal's or variant) angina. Whether this effect plays any role in classical angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

2) Reduction of oxygen utilization: PROCARDIA regularly reduces arterial pressure at rest and at a given level of exercise by dilating peripheral arterioles and reducing the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements and probably accounts for the effectiveness of PROCARDIA in chronic stable angina.

Pharmacokinetics and Metabolism: PROCARDIA is rapidly and fully absorbed after oral administration. The drug is detectable in serum 10 minutes after oral administration, and peak blood levels occur in approximately 30 minutes. It is highly bound by serum proteins. PROCARDIA is extensively converted to inactive metabolites and approximately 80% of PROCARDIA and metabolites are eliminated via the kidneys. The half-life of nifedipine in plasma is approximately two hours. There is no information on the effects of renal or hepatic impairment on excretion or metabolism of PROCARDIA.

Hemodynamics: Like other slow channel blockers, PROCARDIA exerts a negative inotropic effect on isolated myocardial tissue. This is rarely, if ever, seen in intact animals or man, probably because of reflex responses to its vasodilating effects. In man, PROCARDIA causes decreased peripheral vascular resistance and a fall in systolic and diastolic pressure, usually modest (5–10 mm Hg systolic), but sometimes larger. There is usually a small increase in heart rate, a reflex response to vasodilation. Measurements of cardiac function in patients with normal ventricular function have generally found a small increase in cardiac index without major effects on ejection fraction, left ventricular end diastolic pressure (LVEDP) or volume (LVEDV). In patients with impaired ventricular function, most acute studies have shown some increase in ejection fraction and reduction in left ventricular filling pressure.

Electrophysiologic Effects: Although, like other members of its class, PROCARDIA decreases sinoatrial node function and atrioventricular conduction in isolated myocardial preparations, such effects have not been seen in studies in intact animals or in man. In formal electrophysiologic studies, predominantly in patients with normal conduction systems, PROCARDIA has had no tendency to prolong atrioventricular conduction, prolong sinus node recovery time, or slow sinus rate.

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of PROCARDIA would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. See Warnings.

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: See Indications and Warnings. Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy category C: Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times the maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well-controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: In multiple-dose U.S. and foreign controlled studies in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of PROCARDIA.

Adverse Effect	PROCARDIA (%) (N = 226)	Placebo (%) (N = 235)
Dizziness, lightheadedness, giddiness	27	15
Flushing, heat sensation	25	8
Headache	23	20
Weakness	12	10
Nausea, heartburn	11	8
Muscle cramps, tremor	8	3
Peripheral edema	7	1
Nervousness, mood changes	7	4
Palpitation	7	5
Dyspnea, cough, wheezing	6	3
Nasal congestion, sore throat	6	8

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The most common adverse events were the same ones seen in the controlled trials, with dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

Several of these side effects appear to be dose related. Peripheral edema occurred in about one in 25 patients at doses less than 60 mg per day and in about one patient in eight at 120 mg per day or more. Transient hypotension, generally of mild to moderate severity and seldom requiring discontinuation of therapy, occurred in one of 50 patients at less than 60 mg per day and in one of 20 patients at 120 mg per day or more.

In addition, 2% or fewer of patients reported the following. **Respiratory:** Nasal and chest congestion, shortness of breath. **Gastrointestinal:** Diarrhea, constipation, cramps, flatulence. **Musculoskeletal:** Inflammation, joint stiffness, muscle cramps. **CNS:** Shakiness, nervousness, jitteriness, sleep disturbances, blurred vision, difficulties in balance. **Other:** Dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving PROCARDIA with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of PROCARDIA treated patients (see **Precautions**).

In a subgroup of patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

OVERDOSAGE: Although there is no well documented experience with PROCARDIA overdosage, available data suggest that gross overdosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to PROCARDIA overdosage calls for active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Clearance of PROCARDIA would be expected to be prolonged in patients with impaired liver function. Since PROCARDIA is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION: The dosage of PROCARDIA needed to suppress angina and that can be tolerated by the patient must be established by titration. Excessive doses can result in hypotension.

The starting dose is one 10 mg capsule, swallowed whole, 3 times/day. The usual effective dose range is 10–20 mg three times daily. Some patients, especially those with evidence of coronary artery spasm, respond only to higher doses, more frequent administration, or both. In such patients, doses of 20–30 mg three or four times daily may be effective. Doses above 120 mg daily are rarely necessary. More than 180 mg per day is not recommended.

In most cases, PROCARDIA titration should proceed over a 7–14 day period so that the physician can assess the response to each dose level and monitor the blood pressure before proceeding to higher doses.

If symptoms so warrant, titration may proceed more rapidly provided that the patient is assessed frequently. Based on the patient's physical activity level, attack frequency, and sublingual nitroglycerin consumption, the dose of PROCARDIA may be increased from 10 mg t.i.d. to 20 mg t.i.d. and then to 30 mg t.i.d. over a three-day period.

In hospitalized patients under close observation, the dose may be increased in 10 mg increments over four to six-hour periods as required to control pain and arrhythmias due to ischemia. A single dose should rarely exceed 30 mg.

No "rebound effect" has been observed upon discontinuation of PROCARDIA. However, if discontinuation of PROCARDIA is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.

Co-Administration with Other Antianginal Drugs: Sublingual nitroglycerin may be taken as required for the control of acute manifestations of angina, particularly during PROCARDIA titration. See **Precautions, Drug Interactions,** for information on co-administration of PROCARDIA with beta blockers or long-acting nitrates.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains 10 mg of nifedipine. PROCARDIA Capsules are supplied in bottles of 100 capsules (NDC 0069-2600-66), and unit dose (10x10) capsules (NDC 0069-2600-41).

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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GUEST SPEAKERS

LONNIE R. BRISTOW, MD
President, American Society of Internal Medicine, San Pablo, CA
- **Reimbursement in the 1980s**

ROGER DWORKIN, JD
Professor, School of Law Indiana University Bloomington, IN
- **The Issue of Wrongful Life**

ALAN N. HOWARD, PhD
Department of Medicine Addenbrookes Hospital Cambridge, England
- **Obesity—An Overview of Causes, Complications & Control**

JAY H. KRACHMER, MD
Professor of Ophthalmology University of Iowa Hospital Iowa City, IA
- **Pseudophakic Bullous Keratopathy**
- **Control & Correction of Astigmatism in Cataract & Penetrating Keratoplasty Surgery**

MELVIN MARCUS, MD
Professor of Medicine University of Iowa Hospital Iowa City, IA
- **Evaluation of Patient with Possible Cardiac Chest Pain**

GERALD B. RICH, MD
Head, Department of Neurology & Sleep Disorders Good Samaritan Hospital Portland, OR
- **Psychological Aspects of the Disorders of Sleep**

JOHN L. WOBIG, MD
Chief, Ocular Plastics University of Oregon Portland, OR
- **Diagnosis & Treatment of Nasolacrimal Disorders in Infants**

SCIENTIFIC SESSIONS

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(Continued from Page 40)

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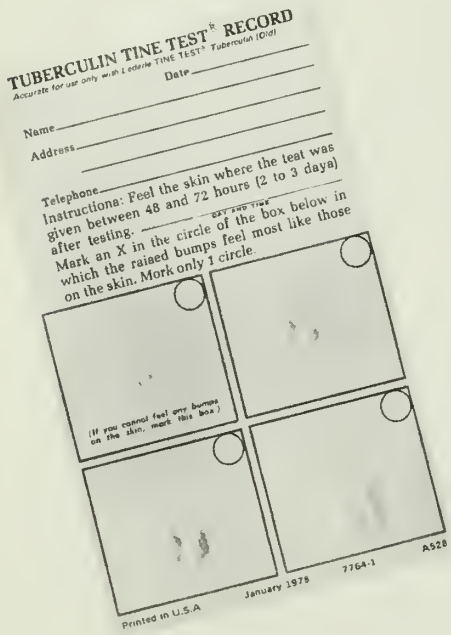

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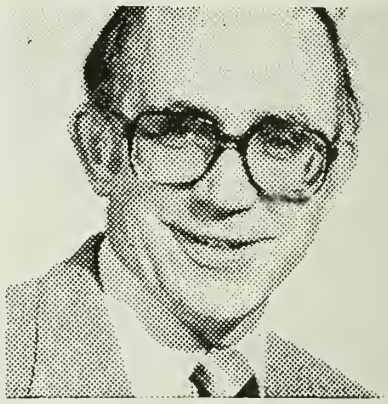

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(Continued from Page 34)

Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II, MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

ɔruary 28-March 4—**Purgatory Ski Symposium.** Durango, Colorado. Monday-Friday. Tamaron Lodge. 20 credit hours, also AAFP. Contact: Gwenn Robinson,MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

REGON

The following list of continuing medical education offerings n the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

EDICAL GRAND ROUNDS

uglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

anuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

od Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

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and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

September 10-11—**Ashland Conference: Antimicrobial Therapy in Perspective: The Place of the New Drugs.** Ashland. Friday-Saturday. Ashland Hills Inn. For information contact: OHSU-CME.

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

(Continued on Page 56)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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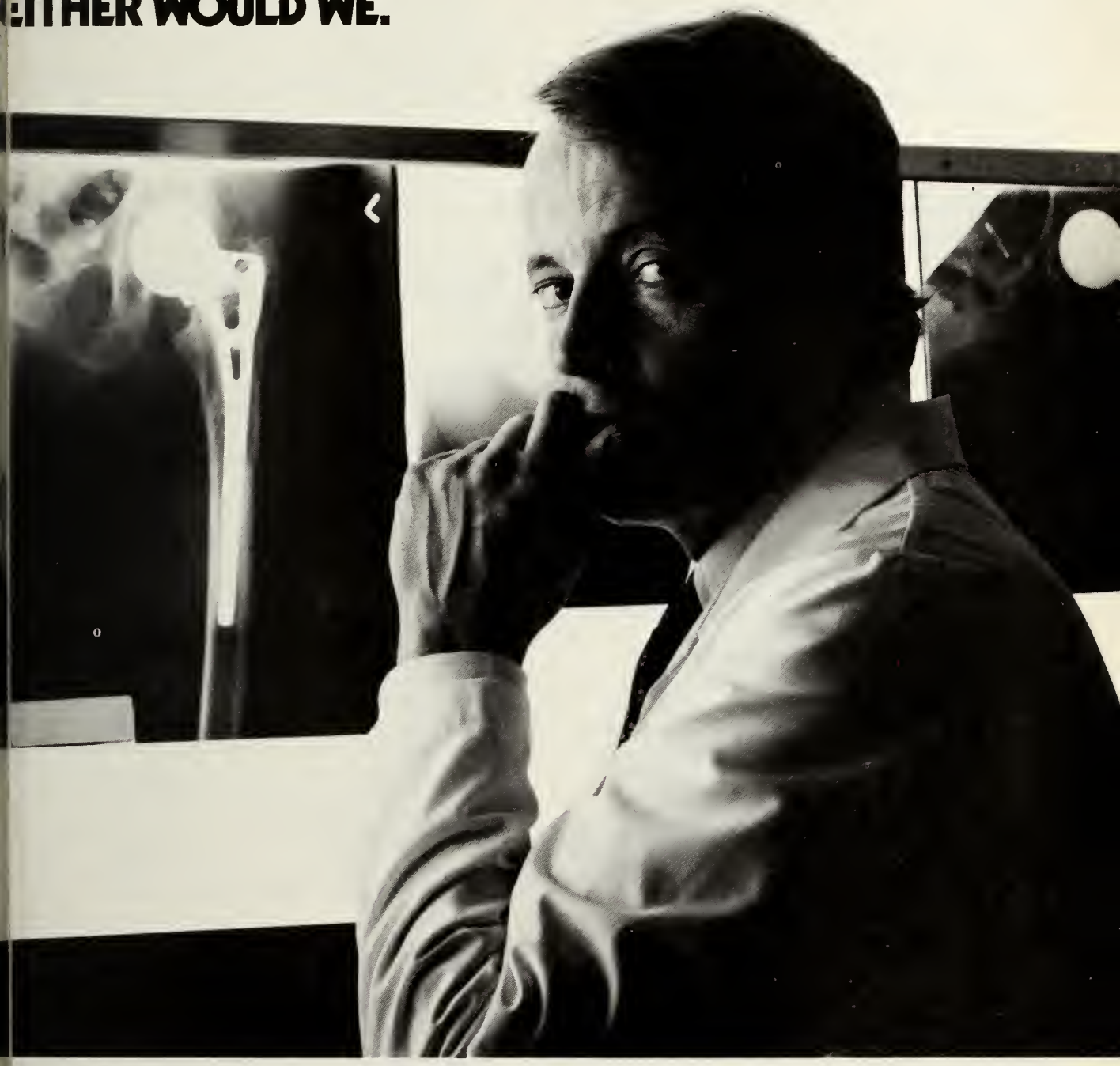

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(Continued from Page 54)

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Friday—7:30-8:30 a.m. Contact: Thomas Schwenk, MD, (801) 350-4111.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

September 15-17—**Annual Utah State Medical Association Meeting** (Sponsors: University of Utah/Utah State Medical Association). Salt Lake City. Wednesday-Friday. Hotel Utah. Fee: To be announced. Credit: To be announced. Contact: Maxcine Fry (801) 355-7477.

September 17—**Pediatric Ophthalmology Meeting: Eye Problems of Children** (Sponsor: University of Utah). Snowbird. Friday. 6 hrs. Fee: $15-$35. Contact: Jane Kivlin, MD (801) 581-6384.

October 6-9—**Child Neurology** (Sponsor: University of Utah). Salt Lake City. Wednesday-Saturday. Hotel Utah. 30 hrs. Fee: To be announced. Contact: Jack Madsen, MD (801) 581-7624.

November 12-13—**New Techniques in Pulmonary Medicine** (Sponsors: LDS Hospital/University of Utah). Salt Lake City. Friday-Saturday. Little America. 10 hrs. $70. Contact: C. Duane Schmidt, MD (801) 353-8201.

January 21-23—**7th Annual U of U Seminar on Sexual Function/Dysfunction** (Sponsor: University of Utah). Park City. Friday-Sunday. 19 hrs. Fee: $200. Contact: Claire Turner (801) 581-5809.

January 26-February 3—**Air Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. Credit and fee to be announced. Contact: Dennis C. Brimhall, MD (801) 581-2682.

January 31-February 4—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. $350. Contact: John Matsen, MD (801) 581-5514.

February 14-17—**12th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 28 hrs. $280. Contact: Linda Twitchell (801) 581-8633.

February 18-22—**28th Annual Postgraduate Course in Anesthesiology** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hilton Hotel. 17 hrs. Fee to be announced. Contact: Ted Stanley, MD (801) 581-7647.

February 19-22—**24th Annual Ob/GYN Postgrad Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 23-26—**Perinatal Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

September 16-17—**Plastic Repair and Wound Management.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

September 16-18—**(WYOMING) Cytology Continuing Education Workshop.** Jackson. Thursday-Saturday. Contact: CME Harborview.

September 23-25—**Cytology Continuing Education Workshop.** Renton. Thursday-Saturday. Valley General Hospital. Contact: CME Harborview.

September 23-25—**Advances in Internal Medicine.** Seattle. Thursday-Saturday. Westin Hotel. Contact U/W.

September 24—**Pathology Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

September 24-25—**Immediate Care of Sick and Injured.** Seattle. Friday-Saturday. U/W Health Sciences Center. Contact: U/W.

September 24-25—**Sudden Infant Death Syndrome and Infant Apnea: Current Questions and Management Topics.** Seattle. Friday-Saturday. Children's Orthopedic Hospital and Medi-

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

cal Center. Contact: Patty Knudsen, SIDS/Apnea Office, Children's Orthopedic Hospital and Medical Center, PO Box C5371, Seattle, WA 98105. (206) 634-5323.

September 24-26—**(CANADA) Ethics in Clinical Medicine.** Victoria, BC. Friday-Sunday. Empress Hotel. Contact: U/W.

September 24-26—**American Society for Adolescent Psychiatry —Western Regional Meeting.** Seattle. Friday-Sunday. Park Hilton Hotel. 12 hrs Category 1 credit. Contact: Richard O. Gode, MD, Program Chairman, 4026 NE 55th, Seattle, WA 98105. (206) 523-8940.

September 30-October 1—**Neuroendrocrinology.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

October 1-2—**Otolaryngology for Non-Otolaryngologists.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 7-10—**Annual Meeting, Washington State Medical Association.** Yakima. Thursday-Sunday. Yakima Convention Center, The Towne Plaza, and The Holiday Inn. Contact: Marcia Wahlman, Convention Coordinator, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

October 8-9—**Annual Cancer Conference: Symptom Management in the Cancer Patient.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 15-16—**The Insulin Pump in Clinical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 20-22—**Advances in Internal Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

October 21-22—**Nosocomial Infections and Herpes/Hepatitis.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

October 22—**Gynecologic Surgery.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 22-23—**Care and Rehabilitation of the Injured Wrist.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 28-29—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

November 4-5—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 5—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

November 5-6—**Outpatient Surgical Care.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 12—**Eye Care in General Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 12-13—**Diabetes. Seattle.** Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

November 13—**Medicine and Religion.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

November 18-19—**Psychiatric Emergencies.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 19—**Neuroophthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 20-27—**(HAWAII) 3 For 1: Proctology, Psychiatry, Principles.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

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November 20-27—**(HAWAII) Financial Planning.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

December 2-3—**Surgical Aspects of Lung Disease.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

December 3—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 4—**Orthopaedics for Attorneys.** Seattle. Saturday. Sheraton Hotel: Contact: U/W.

December 6-7—**American College of Physicians MKSAP IV.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

December 9-10—**Aging and Elderly.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: U/W.

January 13-14—**Sex and the Family.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

January 20-21—**Cytology.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

January 21-22—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 21-23—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 23—**Dyslexia.** Seattle. Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 27-28—**Beta Blockers and Calcium Antagonists.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

January 29-30—**Benefits and Problems of Exercise.** Seattle. Saturday-Sunday. Swedish Hospital. Contact: U/W.

February 3-4—**Ultrasound/Echocardiography.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 4-5—**Diseases of the Elderly.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 5-12—**(IDAHO) Management of Pain.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 12-19—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 14-18—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Friday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 17-18—**Soft Tissue Surgery.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 19-26—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Contact: U/W.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-March 5—**(IDAHO) Sports Medicine 83.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 4-5—**High-Risk Infants of the 1980s.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

March 5-12—**(IDAHO) Management of Obesity.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 10-11—**Nutrition and Bone Metabolism.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

March 12-19—**(HAWAII) Office Gynecology.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

March 16-18—**MKSAP: Medical Knowledge Self-Assessment Program.** Seattle. Wednesday-Friday Virginia Mason Medical Center. Contact: VMMC.

March 18—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

March 18-19—**Recent Developments in Occupational Medicine.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 19-26—**(HAWAII) Advances in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 25-26—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 26-April 2—**(HAWAII) Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Pathology Day.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

April 1-2—**Compensation Law/Public Policy/Back Pain.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 8-9—**Management of Obesity. Seattle.** Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 11-22—**Rehabilitation Medicine Review.** Seattle. Sunday-Thursday. Sheraton. Contact: U/W.

April 14-15—**Vascular Disease/Primary MDs.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

April 22-24—**Office Laboratory Diagnosis for the Clinician.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

April 28-29—**Financial Planning for Physicians.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

May 6-7—**Advances in Behavioral Medicine.** Seattle. Thursday-Friday. Swedish Hospital. Contact: U/W.

May 13—**Medical Alumni Day.** Seattle. Thursday. U/W Health Sciences Building. Contact: U/W.

May 13-14—**Hypertension.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 14—**Sexually Transmitted Diseases in Homosexual Men.** Seattle. Friday. Swedish Hospital. Contact: U/W.

May 19-21—**Office Management of Joint Disease.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

May 20-21—**Prescription and Nonprescription Drugs.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 26-27—**Benefits/Problems of Exercise in Women.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

May 26-27—**Clinical Neurogenetics.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

June 2-3—**Managerial Skills.** Seattle. Wednesday-Thursday. Children's Orthopedic Hospital. Contact: U/W.

June 3—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

June 3-4—**Acute Medical Problems.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

June 9-11—**Common Office Procedures.** Seattle. Wednesday-Friday. U/W Health Sciences Building. Contact: U/W.

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: 1983—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: May 19-21, 1983, Doubletree Inn, Tucson.

California Medical Association—731 Market St., San Francisco 94103. (415) 777-2000. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. (303) 861-1221. Annual Meeting: September 21-24, 1982, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1983: date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 30-October 2, 1982, Sheraton, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 12-15, 1983, Elko Convention Center, Elko.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 247-0539. Annual Meeting: May 4-6, 1983. Four Seasons Motor Hotel, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 14-17, 1982, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Winter Seminar: January 21-22, 1983, Rawlins; Annual Meeting: June 29-July 2, 1983, Jackson Lake Lodge, Moran.

(Continued from Page 58)

June 16-17—**Human Immunogenics.** Seattle. Wednesday-Thursday. Seattle. U/W Health Sciences Building. Contact: U/W.

June 22-24—**Burn.** Seattle. Tuesday-Thursday. Sheraton Hotel. Contact: U/W.

June 23-24—**Nosocomial Infections Herpes Hepatitis.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

June 27-29—**(OREGON) Office Management of Common Psychiatry Problems.** Sun River. Sunday-Tuesday. Sun River Hotel. Contact: U/W.

June 30-July 1—**(OREGON) Arts and Medicine.** Ashland. Wednesday-Thursday. Southern Oregon State College. Contact: U/W.

July 21-22—**American College of Physicians MKSAP VI.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

July 28-30—**Debates in Otolaryngology.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

July 29-31—**Washington State Society of Anesthesiologists: Seafair V Anesthesia Meeting.** Seattle. Sheraton. Contact: Washington State Society of Anesthesiology, Marcia Wahlman, Executive Secretary, 2033 Sixth Avenue, Suite 900, Seattle, WA 98212. (206) 623-4801.

August 4-5—**Sports Medicine Summer 1983.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

August 25-26—**Urology for Urologists.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

WYOMING

See Washington listing, September 16-18, 1982.

January 21-22—**Wyoming Medical Society Winter Seminar.** Rawlins. Friday-Saturday. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

June 29-July 2—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

Index to
The Western Journal of Medicine Advertising

ARCO SURGICAL INSTRUMENTS 39
AYERST LABORATORIES
Premarin Tabs/Vag Cream 17, 18, 19, 20
BIO-SCIENCE ENTERPRISES 48
BIO-SCIENCE LABORATORIES
Launches service in Greater/Seattle area 39
BORNING CORP, THE
Borning's new 650 H-R 13
BRISTOL LABORATORIES
CME Program 5
CALIFORNIA MEDICAL ASSOCIATION
112th Annual Session 49
CLASSIFIED 38, 40, 50
COOPERATIVE OF AMERICAN PHYSICIANS, THE
Mutual Protection Trust 3
CPS MEDICAL BILLING 15
DESERT SPRING HOSPITAL OF LAS VEGAS
Symposium—Gastrointestinal Biliary Disease 2
DOCTORS' CO., THE 55
ELI LILLY & CO.
Keflex 59
HOSPITAL OF THE GOOD SAMARITAN, THE
Cancer Symposium 24
Diabetes Symposium 57
KEY PHARMACEUTICALS
Theo-Dur 22, 23, 24
LEDERLE LABORATORIES
TB TINE 51, 52
NORCAL MUTUAL INSURANCE CORPORATION 6
PFIZER
Procardia 26, 27, 28, 29, 30, 43, 44
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 31
PRACTICE SERVICE CORPORATION 35
PROFESSIONAL BUSINESS SERVICE INC. 45
PROFESSIONAL COMPUTER STORE 49
RESEARCH INDUSTRIES INC.
Rimso-50, Rimso-100 33
ROCHE LABORATORIES
Bactrim ..... 2nd Cover, 1, 2
Limbitrol ..... 3rd and 4th Covers
ST. MICHAELS UNIVERSITY SCHOOL 52
SCHOOL OF MEDICINE OREGON HEALTH SCIENCES UNIVERSITY
Continuing Medical Education 53
SMITH KLINE & FRENCH LABORATORIES
Dyazide 36
E. R. SQUIBB & SONS, INC.
Corgard 8, 9, 10
STAFF RESOURCES INC. 2
3M CLINICAL LABORATORY SERVICES 37
UNIVERSITY OF HAWAII
A series of CME courses in China 53
UPJOHN CO., THE
Motrin 25
U.S. AIR FORCE 39
WASHINGTON STATE MEDICAL ASSOCIATION ANNUAL MEETING 46,47
WYETH LABORATORIES
Lo/Ovral 41, 42

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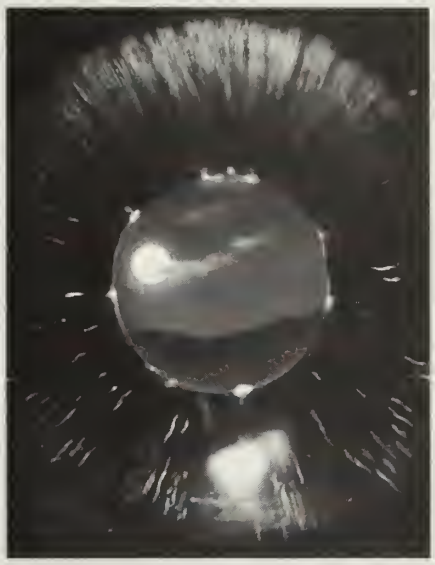

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prolongation of conduction time reported with use of
lic antidepressants, especially high doses Myocar-
nfarction and stroke reported with use at this class of
) Caution patients about possible combined effects
alcohol and other CNS depressants and against haz-
s occupations requiring complete mental alertness
operating machinery, driving)
***Usage in Pregnancy*: Use of minor tranquilizers**
luring the first trimester should almost always
e avoided because of increased risk of con-
enital malformations as suggested in several
tudies. Consider possibility of pregnancy when
nstituting therapy; advise patients to discuss
herapy if they intend to or do become pregnant.
physical and psychological dependence to chlor-
oxide have been reported rarely, use caution in
nistering Limbitrol to addiction-prone individuals or
who might increase dosage, withdrawal symptoms
ring discontinuation of either component alone have
reported (nausea, headache and malaise for amitrip-
symptoms [including convulsions] similar to those
bitrate withdrawal for chlordiazepoxide)
utions: Use with caution in patients with a history
zures, in hyperthyroid patients or those on thyroid
ation, and in patients with impaired renal or hepatic
on Because of the possibility of suicide in depressed
ts, do not permit easy access to large quantities in
patients Periodic liver function tests and blood
s are recommended during prolonged treatment
ptyline component may block action of guanethidine
ilar antihypertensives Concomitant use with other
atropic drugs has not been evaluated sedative
may be additive Discontinue several days before
y Limit concomitant administration of ECT to essen-
atment See Warnings for precautions about preg-
Limbitrol should not be taken during the nursing
Not recommended in children under 12 In the
and debilitated, limit to smallest effective dosage to
de ataxia, oversedation, confusion or anticholinergic
se Reactions: Most frequently reported are those associated with either component alone drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs

Cardiovascular Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido

Neurologic Incoordination, ataxia numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns

Anticholinergic Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract

Allergic Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus

Hematologic Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Endocrine Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels

Other Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling

Overdosage: Immediately hospitalize patient suspected of having taken an overdose Treatment is symptomatic and supportive IV administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning See complete product information for manifestation and treatment

Dosage: Individualize according to symptom severity and patient response Reduce to smallest effective dosage when satisfactory response is obtained Larger portion of daily dose may be taken at bedtime Single *h s* dose may suffice for some patients Lower dosages are recommended for the elderly Limbitrol 10-25, initial dosage of three to four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required Limbitrol 5-12 5, initial dosage of three to four tablets daily in divided doses, for patients who do not tolerate higher doses

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12 5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10, Prescription Paks of 50

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Manati, Puerto Rico 00701

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Artist's conception, looking out from the human eye as conceived in a schematic model.

In anxious depression

Limbitrol® IV

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

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For broad symptom response, including insomnia

ROCHE®

Before prescribing, please see summary of product information on preceding page.

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VOLUME 137 • NUMBER 4 **OCTOBER 1982**

ORIGINAL ARTICLES

273 *Recent Progress in the Treatment of Epithelial Ovarian Malignancy*
JONATHAN S. BEREK, MD; NEVILLE F. HACKER, MD, and LEO D. LAGASSE, MD

278 *Fragile X-Linked Mental Retardation and Macro-orchidism*
BYRON C. MOORE, EdD; THOMAS W. GLOVER, PhD; BARBARA KAISER-McCAW, PhD, and FREDERICK HECHT, MD

282 Amanita phalloides-*Type Mushroom Poisoning*
KENT R. OLSON, MD; SUSAN M. POND, MB, MD; JAMES SEWARD, MD; KATHY HEALEY, PharmD; OLGA F. WOO, PharmD, and CHARLES E. BECKER, MD

MEDICAL PROGRESS

290 *Nuclear Magnetic Resonance Imaging: Current Capabilities*
PETER L. DAVIS, MD; LAWRENCE E. CROOKS, PhD; ALEXANDER R. MARGULIS, MD, and LEON KAUFMAN, PhD

SPECIALTY CONFERENCE

294 *Are Volcanoes Hazardous to Your Health? What Have We Learned From Mount St Helens?*
Discussant: A. SONIA BUIST, MD

MEDICAL STAFF CONFERENCE

302 *Immunoglobulin A and the Kidney* Chief Discussant: JAMES L. NAUGHTON, MD

EPITOMES OF PROGRESS

310 *Neurology—Important Advances in Clinical Medicine*

EDITORIALS

317 • *Thoughts on the Past, Present and Futureof* WJM • *NMR: Diagnostic Wave of the Future*
• *Poison Control Centers—A Vital Community Resource*

CASE REPORTS

322 *Peritoneal Dialysis for Isopropanol Poisoning* MARK B. MECIKALSKI, MD, and THOMAS A. DEPNER, MD

325 *Hematologic Improvement Following Splenectomy for Hemoglobin-H Disease*
GAIL M. WAGNER, MD; STEPHEN A. LIEBHABER, MD; HUNTER O. CUTTING, MD, and STEPHEN H. EMBURY, MD

328 *Aminophylline-Induced Exfoliative Dermatitis: Cause and Implications*
DAVID W. NIERENBERG, MD, and FREDERICK S. GLAZENER, MD

331 *The Clinical Features of Covert Diuretic Use* DANIEL I. SPRATT, MD, and ALLAN PONT, MD

335 *Isolated Cortical Blindness in Pregnancy* ROBERT N. NISHIMURA, MD, and RICHARD KOLLER, MD

CORRESPONDENCE

338 • *Patients With Cervical Cancer; With Reply by Authors* • *Radiology and Medical Care Costs*
• *Waterborne Transmission of* Campylobacter • *The Pot and the Kettle*

TOPICS IN PRIMARY CARE MEDICINE

340 *Shoulder Pain* RICHARD H. WHITE, MD

HEALTH CARE DELIVERY

346 *A Model Poison Control System*
THEODORE G. TONG, PharmD; CHARLES E. BECKER, MD; DONNA FOLIART, MD, MPH, and LINDA MORSE, MD, MPH

351 *Medical Evaluation Before Operation* DIANE L. ELLIOT, MD; DOUGLAS H. LINZ, MD, and JOSEPH A. KANE, MD

COMMENTARY

359 *Commentary From Coeur d'Alene: Care for Terminally Ill Patients* E. R. W. FOX, MD

361 *Book Reviews*

363 *In Memoriam*

Medical Practice Questions, See Pages 277, 337 and 360
Detailed Table of Contents, See Advertising Pages 7 and 11
Information for Authors, See August Issue, Advertising Page 54

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING** (See Advertising Page 12)

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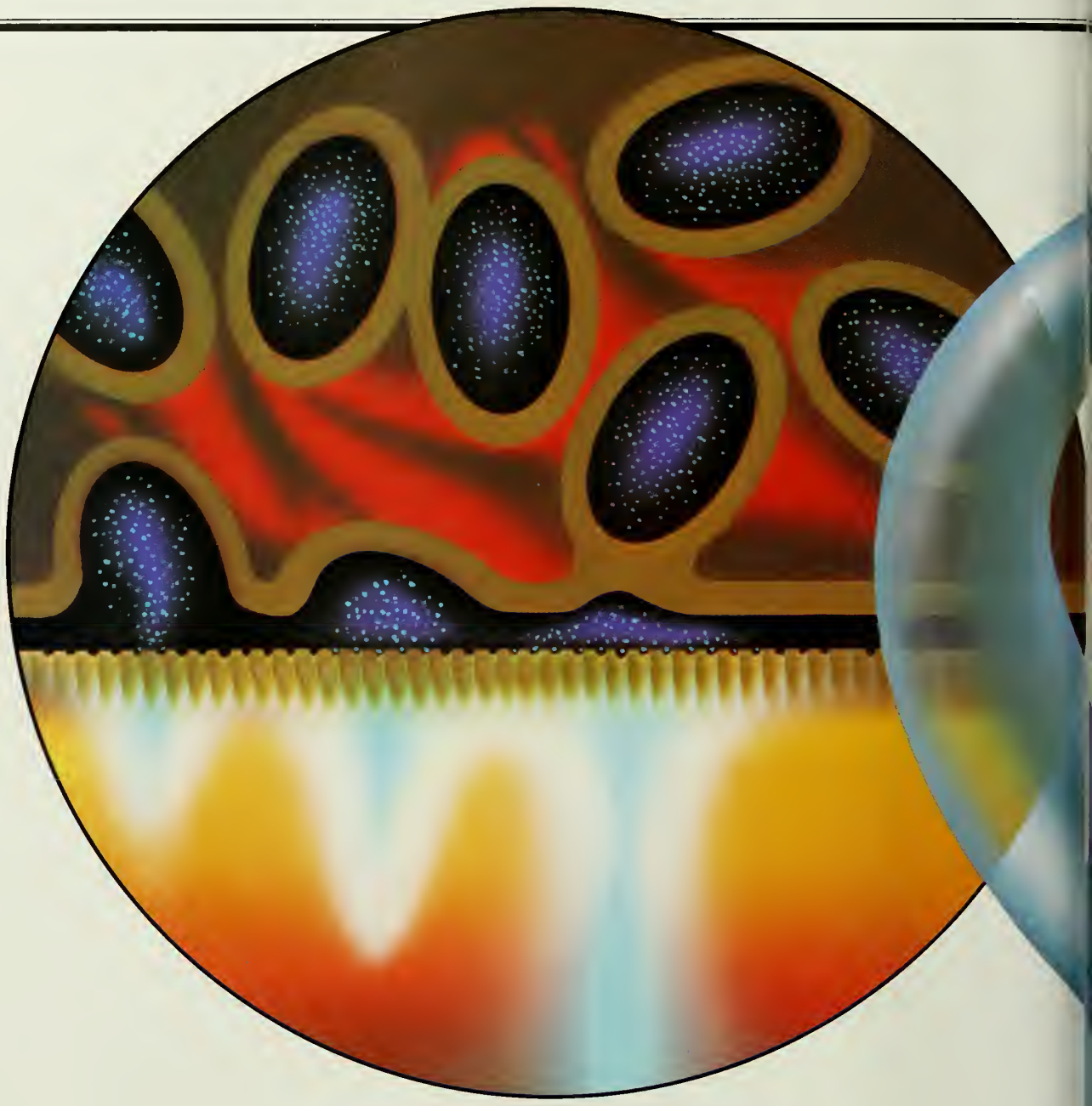
VALIUM® (diazepam/Roche) IN THE FOREFRONT OF NEURORECEPTOR RESEARCI



Artist's concept of neurotransmitter being released into synaptic cleft and impinging on receptor sites

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Opening new investigative pathways into where and how Valium (diazepam/Roche) exerts its distinctive antianxiety action

New discoveries in receptor research have stimulated the search for endogenous brain substances that may be involved in the mediation of anxiety.[1-5] It has been further theorized that these substances may act as ligands that bind to the same or similar sites as do benzodiazepine molecules[5,6]—binding sites early identified with the use of ^{3}H-diazepam.[5,7] These binding sites are now postulated to be benzodiazepine receptors, since the ability of benzodiazepines to bind with the sites appears to correlate with their clinical effects.[2,4,7,8]

Present investigations into clinical relevance of binding sites. Laboratories at Roche have conducted research to identify and isolate substances that may prove to be endogenous ligands, but no definitive identification has yet been made. Researchers are also studying substances which do not bind, but rather interact with the benzodiazepine binding sites—most notably gamma-aminobutyric acid (GABA)—and are postulated to mediate certain pharmacologic and clinical benzodiazepine effects.[2-4,9,10]

Under especially intense investigations are the GABA receptors and the benzodiazepine binding sites themselves—apparently constellations of closely linked but not identical structures.[8]

Future implications for improved therapy. In future work, Roche researchers and other scientists hope to identify and characterize various differential sites in the brain, which may result in more specific diagnostic and therapeutic approaches.

Valium® Ⓘⓥ 2-mg, 5-mg, 10-mg scored tablets

diazepam/Roche

THE RESEARCH AND CLINICAL LEADER

Please see brief summary of product information and references on the following page.

ROCHE®

VALIUM® IV
(diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. Initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500;* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25† and in boxes containing 10 strips of 10.†

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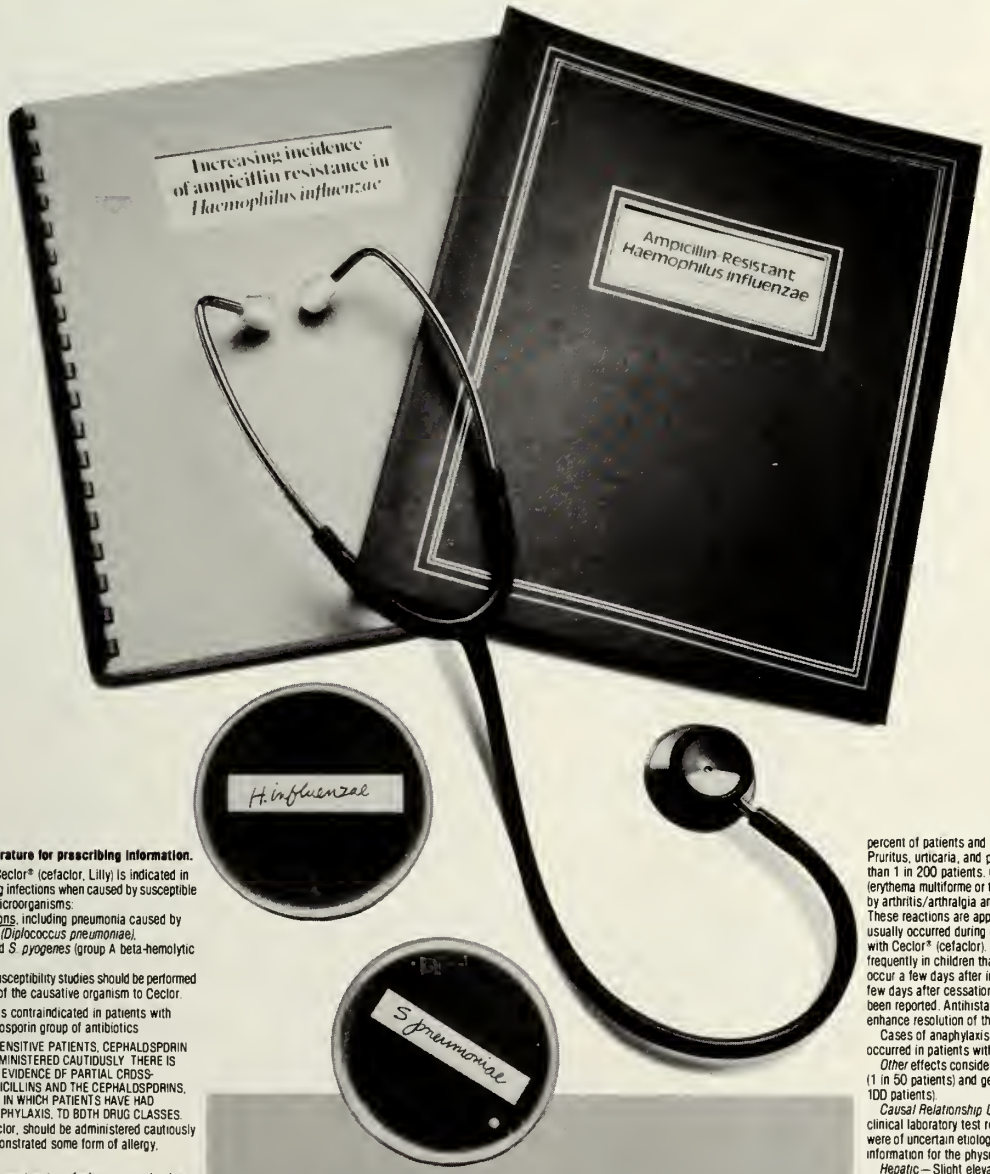
An added complication... in the treatment of bacterial bronchitis*



Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. Influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae,* and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor® (cefaclor). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200). [100281R]

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.®

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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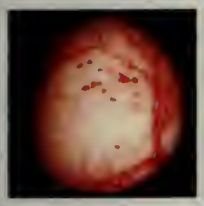
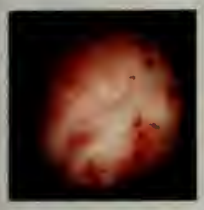
SYMPTOMS:

EARLY INTERSTITIAL CYSTITIS



- ☐ irritative voiding symptoms
- ☐ suprapubic pain
- ☐ functional bladder capacity reduced
- ☐ anatomical bladder capacity:
  - EARLY — normal
  - CLASSICAL — reduced

CLASSICAL INTERSTITIAL CYSTITIS



- ☐ vesical mucosa:
  - EARLY — normal appearing
  - CLASSICAL — ulcerated, scarred
- ☐ submucosal vesical hemorrhages observed following second overdistension

DIAGNOSIS: INTERSTITIAL CYSTITIS

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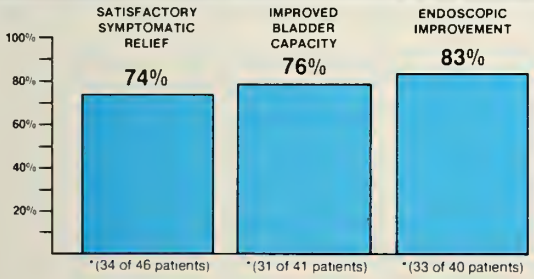
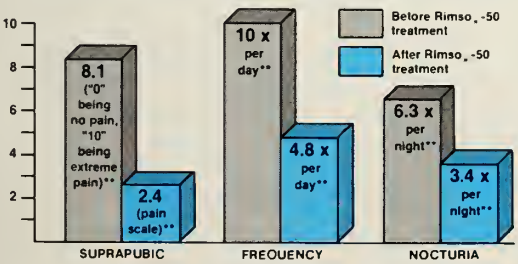


* STEWART, B H., et al., J. Urol., 36 116, 1976



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INDICATIONS AND USAGE: Rimso-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS: None known.

WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso-50. The physician should be cognizant of this possibility in prescribing Rimso-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

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*Stewart, B H., et al., J. Urol., 36.116, 1976

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THE WESTERN
Journal of Medicine

VOLUME 137 • NUMBER 4 **OCTOBER 1982**

TABLE OF CONTENTS

ORIGINAL ARTICLES

273 *Recent Progress in the Treatment of Epithelial Ovarian Malignancy*
JONATHAN S. BEREK, MD; NEVILLE F. HACKER, MD, and LEO D. LAGASSE, MD
From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, UCLA School of Medicine and The Center for Ovarian Cancer of the Jonsson Comprehensive Cancer Center, Los Angeles.

278 *Fragile X-Linked Mental Retardation and Macro-orchidism*
BYRON C. MOORE, EdD; THOMAS W. GLOVER, PhD; BARBARA KAISER-McCAW, PhD, and FREDERICK HECHT, MD
From the Department of Special Education, Arizona State University, and the Genetics Center, Southwest Biomedical Research Institute, Tempe, Arizona.

282 Amanita phalloides-*Type Mushroom Poisoning*
KENT R. OLSON, MD; SUSAN M. POND, MB, MD; JAMES SEWARD, MD; KATHY HEALEY, PharmD; OLGA F. WOO, PharmD, and CHARLES E. BECKER, MD
From the San Francisco Bay Area Regional Poison Control Center and the Medical Service, San Francisco General Hospital Medical Center; and the Department of Medicine, University of California, San Francisco.

MEDICAL PROGRESS

290 *Nuclear Magnetic Resonance Imaging: Current Capabilities*
PETER L. DAVIS, MD; LAWRENCE E. CROOKS, PhD; ALEXANDER R. MARGULIS, MD, and LEON KAUFMAN, PhD
From the Radiologic Imaging Laboratory, Department of Radiology, University of California, San Francisco.

SPECIALTY CONFERENCE

294 *Are Volcanoes Hazardous to Your Health? What Have We Learned From Mount St Helens?*
Discussant: A. SONIA BUIST, MD
From the Biological Effects of Volcanic Ash Study Center, The Oregon Health Sciences University.
The proceedings of a Medical Grand Rounds of the Department of Medicine, The Oregon Health Sciences University, Portland.

MEDICAL STAFF CONFERENCE

302 *Immunoglobulin A and the Kidney* Chief Discussant: JAMES L. NAUGHTON, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

EPITOMES OF PROGRESS

Neurology—Important Advances in Clinical Medicine
Items of progress in neurology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

310 *Initiation of Anticonvulsant Therapy* GEORGE K. YORK, MD, and ANDREW J. GABOR, MD

311 *Benign Paroxysmal Positional Vertigo* ROBERT W. BALOH, MD

312 *Lorazepam: A New Antiepileptic Drug in Status Epilepticus Therapy* NAI-SHIN CHU, MD

312 *Aspirin Use in Stroke Therapy* FRANK M. YATSU, MD

313 *Treatment of Febrile Convulsions* ARNOLD R. KRIEGSTEIN, MD, PhD

314 *The Role of Valproic Acid in the Management of Seizure Disorders* DORIS A. TRAUNER, MD

314 *Gilles de la Tourette's Syndrome* MICHAEL FRANKEL, MD, and D. FRANK BENSON, MD

315 *Neurologic Complications of Routine Immunization* LAWRENCE STEINMAN, MD

EDITORIALS

317 *Thoughts on the Past, Present and Future of* WJM
MALCOLM S. M. WATTS, MD, Editor, and LLOYD H. SMITH, Jr, MD, Associate Editor

319 *NMR: Diagnostic Wave of the Future* GERALD M. POHOST, MD
Dr. Porost is the Scientific Director of Nuclear Magnetic Resonance, Massachusetts General Hospital, Boston, and Associate Professor of Medicine, Harvard Medical School, Boston.

320 *Poison Control Centers—A Vital Community Resource*
CHARLES E. BECKER, MD, and THEODORE G. TONG, PharmD
Dr. Becker is the Medical Director and Dr. Tong was the Program Director of the San Francisco Bay Area Poison Control Center, San Francisco General Hospital Medical Center, San Francisco.

CASE REPORTS

322 *Peritoneal Dialysis for Isopropanol Poisoning* MARK B. MECIKALSKI, MD, and THOMAS A. DEPNER, MD
From the Division of Nephrology, Department of Internal Medicine, University of California Davis Medical Center, Sacramento. Dr. Mecikalski is now Pulmonary Fellow, Division of Respiratory, Critical Care and Occupational (Pulmonary) Medicine, University of Utah Medical Center, Salt Lake City.

(Continued on Page 11)

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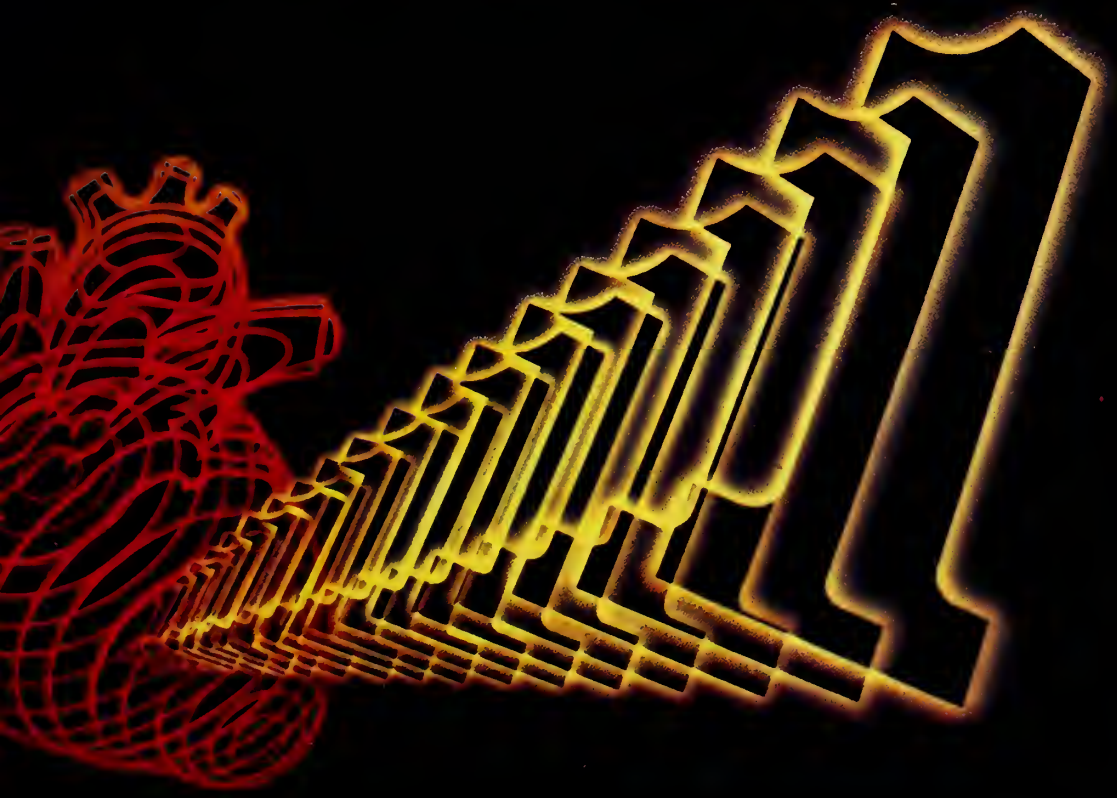

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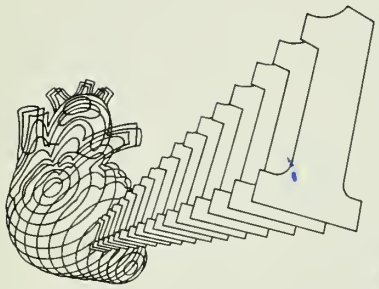

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.
CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).
WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.
OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.
DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.
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(Continued from Page 7)

325 *Hematologic Improvement Following Splenectomy for Hemoglobin-H Disease*
GAIL M. WAGNER, MD; STEPHEN A. LIEBHABER, MD; HUNTER O. CUTTING, MD, and STEPHEN H. EMBURY, MD
From the Department of Medicine, Highland General Hospital, Oakland, California; the Hematology Unit of the Medical Service, San Francisco General Hospital Medical Center, and the Howard Hughes Medical Research Institute and the Department of Medicine, University of California, San Francisco.

328 *Aminophylline-Induced Exfoliative Dermatitis: Cause and Implications*
DAVID W. NIERENBERG, MD, and FREDERICK S. GLAZENER, MD
From the Department of Medicine, Stanford University Medical Center, Stanford, California. Dr. Nierenberg is now Assistant Professor of Medicine and Pharmacology, Dartmouth Medical School, Hanover, New Hampshire.

331 *The Clinical Features of Covert Diuretic Use* DANIEL I. SPRATT, MD, and ALLAN PONT, MD
From the Department of Medicine, Stanford University School of Medicine, Stanford, California, and the Endocrine Clinic, Santa Clara Valley Medical Center, San Jose, California. Dr. Pont is now with the Children's Hospital of San Francisco.

335 *Isolated Cortical Blindness in Pregnancy* ROBERT N. NISHIMURA, MD, and RICHARD KOLLER, MD
From the Department of Neurology, The Oregon Health Sciences University, Portland. Dr. Nishimura is now affiliated with the Veterans Administration Medical Center, Sepulveda, California.

CORRESPONDENCE

Patients With Cervical Cancer

338 HARRISON J. KORNFIELD, MD

338 JOSEPH CHU, MD, MPH, and HISHAM K. TAMIMI, MD, Reply

338 *Radiology and Medical Care Costs* RICHARD M. HEAD, MD

339 *Waterborne Transmission of* Campylobacter
KATHY PERKINS-JONES, BS; ROBERT L. HOLMAN, MS, and FLOYD FROST, PhD

339 *The Pot and the Kettle* JAMES B. SMITH, MD

TOPICS IN PRIMARY CARE MEDICINE

340 *Shoulder Pain* RICHARD H. WHITE, MD
From the Division of General Medicine, Department of Internal Medicine, University of California Davis Medical Center, Sacramento.

HEALTH CARE DELIVERY

346 *A Model Poison Control System*
THEODORE G. TONG, PharmD; CHARLES E. BECKER, MD; DONNA FOLIART, MD, MPH, and LINDA MORSE, MD, MPH
From the San Francisco Bay Area Regional Poison Control Center, the Division of Clinical Pharmacology and Toxicology of the Medical Service and the Northern California Occupational Health Center, all at San Francisco General Hospital Medical Center; the Division of Clinical Pharmacy, School of Pharmacy, and the Department of Medicine, School of Medicine, University of California, San Francisco.

351 *Medical Evaluation Before Operation* DIANE L. ELLIOT, MD; DOUGLAS H. LINZ, MD, and JOSEPH A. KANE, MD
From the Division of General Medicine, Department of Medicine, The Oregon Health Sciences University, Portland.

COMMENTARY

359 *Commentary From Coeur d'Alene: Care for Terminally Ill Patients* E. R. W. FOX, MD
Dr. Fox is in private practice in Coeur d'Alene, Idaho, and is Special Editor for Idaho.

BOOK REVIEWS

361 *Abdominal Radiology*
By JAMES J. McCORT, MD; ROBERT E. MINDELZUN, MD; ROBERT G. FILPI, MD, and CHARLES RENNELL, MD; Edited by JAMES J. McCORT, MD
Reviewed by TIM B. HUNTER, MD

361 *Bone Metastasis—Volume 5 in the series: Metastasis*
Edited by LEONARD WEISS, ScD, MD, PhD, and HARVEY A. GILBERT, MD
Reviewed by CLYDE HELMS, MD

361 *Obstetric Ultrasound: Applications and Principles*
Edited by W. S. VAN BERGEN, MD
Reviewed by MORTON A. STENCHEVER, MD

362 *Cancer of the Head and Neck*
Edited by JAMES Y. SUEN, MD, and EUGENE N. MYERS, MD
Reviewed by THOMAS C. CALCATERRA, MD

362 *Andrews' Diseases of the Skin: Clinical Dermatology—Seventh Edition*
By ANTHONY N. DOMONKOS, MD; HARRY L. ARNOLD, Jr, MD, and RICHARD ODOM, MD
Reviewed by RICHARD B. STOUGHTON, MD

362 *Progress in Perinatal Neurology—Volume 1*
Edited by ROWENA KOROBKIN, MD, and CHRISTIAN GUILLEMINAULT, MD
Reviewed by PEGGY C. FERRY, MD

362 *General Urology—Tenth Edition*
By DONALD R. SMITH, MD
Reviewed by WILLARD E. GOODWIN, MD

363 *In Memoriam*

Medical Practice Questions, See Pages 277, 337 and 360
Subscription Information, See Advertising Page 51
Information for Authors, See August Issue, Advertising Page 54

★ CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA, ALASKA, IDAHO; MONTANA; NEW MEXICO; OREGON UTAH WASHINGTON WYOMING (See Advertising Page 12)

★★ Official Journal of the California Medical Association the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society

CALIFORNIA, HAWAII and NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 139. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

October 15-16—**Advanced Seminar in Urologic Surgery.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

October 15-17—**Neurolinguistic Programming: Sex and Couples Therapy.** Institute of Sexual Behavior and Institute for Medical Education and Research at Village Inn, La Jolla. Friday-Sunday. 18 hrs. $200. Contact: Inst. of Sexual Behavior, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 15-17—**Substance Abuse Prevention Through Effective Parenting.** Isla Vista Health Projects, Inc., and San Diego State Univ. Student Health Services at Village Inn, La Jolla. Friday-Sunday. $150. Contact: Parenting, P.O. Box 9494, San Diego 92109. (714) 272-3126.

October 16—**Review Course for Gynecologic Pathology.** USC at Hilton, Pasadena. Saturday. 6 hrs. $75.

October 16-17—**Thyroid Today—1982, A Clinical Update for the Practicing Physician, First Annual Symposium.** Cypress Foundation at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $130. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

October 16-17—**Medical Psychiatry.** UCSF. Saturday-Sunday. 12½ hrs. $115 before October 1; $135, thereafter. Contact: Aveleen Blumenstock, Cont. Ed., Langley Porter Institute, 401 Parnassus, Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

October 16-23—**4th International Seminar on Operative Arthroscopy.** UCLA at Maui. One week. 38 hrs. $785 with labs; $685, without.

October 17-19—**Dermatology for the Primary Care Physician.** UCD at Holiday Inn Napa. Sunday-Tuesday. 12 hrs. $180.

October 18-25—**Pulmonary Medicine 1982: Advances and American Board Review.** USC at Hilton, Pasadena. One week.

October 20—**New Concepts in Diabetes.** Hospital of the Good Samaritan at Hilton, Los Angeles. Wednesday. 7 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., Hosp. of the Good Samaritan, 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

October 21-23—**California Society of Internal Medicine—Annual Meeting.** MGM Grand, Reno. Thursday-Saturday. Contact: CSIM, 703 Market St., Suite 1412, San Francisco 94103. (415) 362-1548.

October 21-24—**International Symposium on the Mitral Valve.** Scripps Clinic and Research Fndn. at Hotel del Coronado, Coronado. Thursday-Sunday. 23 hrs. $350. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

October 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates, Inc., at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: Ellie Gutman, EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

October 22-24—**Practical Gastroenterology and Flexible Sigmoidoscopy for the Primary Care Physician.** UCSD at Vacation Village, San Diego. Friday-Sunday. 20 hrs. $275. Contact: Howard D. Groveman, MD, UCSD School of Medicine (M-022), La Jolla 92093. (714) 452-4613.

October 22-26—**American Society of Anesthesiologists.** Hilton, Las Vegas. Friday-Tuesday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

October 23—**Current Trends in Cardiovascular Therapy.** Cedars-Sinai Medical Center at Eisenhower Medical Center, Rancho Mirage. Saturday. 8 hrs. $40. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 23-24—**Western Occupational Health Conference—1982.** Western Occupational Medical Assn. at Travelodge at the Wharf, San Francisco. Saturday-Sunday. 10 hrs. $75, members; $95, nonmembers. Contact: WOMA, 433 Palmer Ave., Aptos 95003. (408) 688-9667.

(Continued on Page 14)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

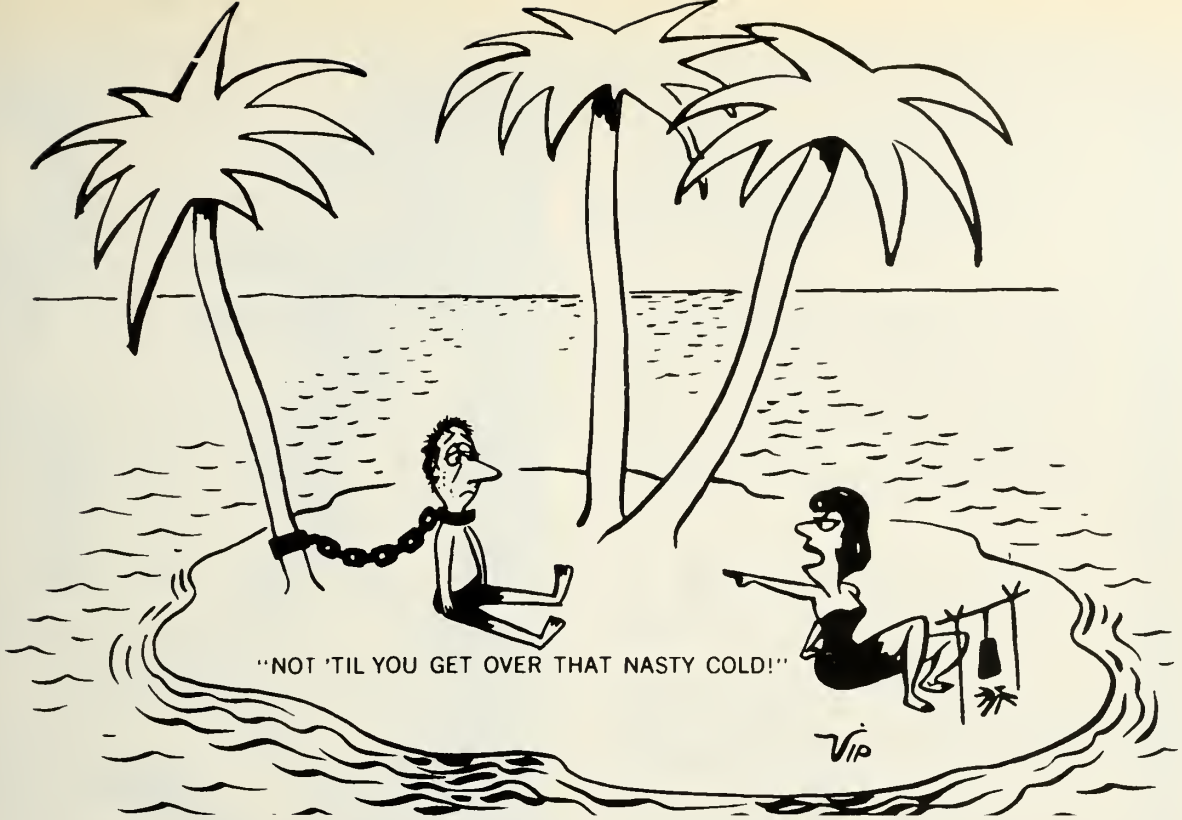
UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.



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(WARNING: May be habit forming)	
Ascorbic Acid	30 mg.
Pheniramine Maleate	2.5 mg.
Pyrilamine Maleate	3.33 mg.
Potassium Citrate	150 mg.

PRECAUTIONS. Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.

CITRA® FORTE CAPSULES

Hydrocodone Bitartrate	5 mg.
(WARNING: May be habit forming)	
Ascorbic Acid	50 mg.
Pheniramine Maleate	6.25 mg.
Pyrilamine Maleate	8.33 mg.
Chlorpheniramine Maleate	1 mg.
Phenylephrine HCl	10 mg.
Salicylamide	227 mg.
Caffeine Alkaloid	30 mg.
Acetophenetidin	120 mg.

PRECAUTIONS. Patients should be advised to avoid using machinery or driving until response to antihistamines is established. Use with caution in patients with idiosyncracies to formula ingredients.
CITRA FORTE CAPSULES should be used with caution in patients with hypertension, cardiac disease, diabetes or hyperthyroidism.
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(Continued from Page 12)

October 23-25—**OB and GYN Endocrinology.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Monday.

October 23-30—**Pediatrics for the Practitioner.** Memorial Hospital Medical Center of Long Beach at Mauna Kea Beach Hotel, Kamuela. One week. 20 hrs. $275. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 24-25—**Meeting of International Strabismological Association and American Association of Pediatric Ophthalmology and Strabismus.** ISA, AAPOS and PMC at Asilomar, Pacific Grove. Sunday-Monday. Contact: PMC.

October 25-28—**7th Annual Family Practice Update.** LLU. Monday-Thursday. 29 hrs. $225.

October 25-29—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

October 27-28—**Vitrectomy.** PMC. Wednesday-Thursday.

October 28-30—**Postgraduate Institute.** CMA at Doubletree Inn, Monterey. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

October 28-30—**2nd Bi-Annual Course in Lower Extremity Trauma: Treatment, Complications and Controversies.** Bone and Joint Disease Foundation at Vacation Village, San Diego. Thursday-Saturday. Contact: Lower Extremity Trauma, P.O. Box 9494, San Diego 92109. (714) 282-9316.

October 28-31—**Obesity and Associated Conditions—32nd Annual Symposium.** American Society of Bariatric Physicians at MGM Grand, Las Vegas. Thursday-Sunday. 17 hrs. $265, members; $315, nonmembers. Contact: ASBP, 5200 S. Quebec, Suite 300, Englewood, CO 80111. (303) 779-4833.

October 29—**Drug Therapy for Heart Disease in the 80's.** UCD at Sacramento Inn, Sacramento. Friday. 6 hrs. $85.

October 29-31—**Arrhythmias and Cardiac Ischemia: Diagnosis and Management.** International Medical Education Corp. at Sahara, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

October 30—**Diagnosis and Treatment of Nasal Disorders.** UCSD. Saturday.

October 30—**Manuel Levin Memorial Cancer Symposium.** Fresno Community Hospital. Saturday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

October 30—**The Troubled Child: Four Practical Approaches.** Del Amo Hospital and American Academy of Pediatrics at Del Amo Hospital, Torrance. Saturday. 4 hrs. $25. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

October 30-November 5—**American Academy of Ophthalmology.** Moscone Center, San Francisco. One week. Contact: AAO, P.O. Box 7424, San Francisco 94115. (415) 921-4700.

November 1-3—**Practical Management of Bronchial Asthma—Symposium II.** Scripps Clinic and Research Fndn. at Rancho Bernardo Inn, San Diego. Monday-Wednesday. 19 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037.

November 1-4—**Interstate Postgraduate Medical Association—Scientific Assembly.** Town and Country, San Diego. Monday-Thursday. 24 hrs. Contact: H. B. Maroney, Exec. Dir., IPMA, P.O. Box 1109, Madison, WI 53701. (608) 257-6781.

November 1-5—**Intensive Care.** STAN. Monday-Friday. 25 hrs. $365.

November 4-5—**Centennial Sterling Bunnell Memorial Lectureship Program—Surgery of the Hand.** UCSF at Letterman Army Institute of Research, San Francisco. Thursday-Friday. 15 hrs. $250.

November 5—**Comprehensive Care of Genitourinary Trauma.** Orange County Urological Soc. and Western Section, American Urological Assn., at Registry Hotel, Irvine. Friday. 8 hrs. Contact: Kathy DeSantis, Western Section, AUA, 21510 S. Main St., Carson 90745. (213) 549-3470.

November 5-6—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Islandia Hyatt, San Diego. Friday-Saturday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80112. (800) 525-8651.

November 6—**The Sexually Active Adolescent—Implications for the Health Care Professional.** UCLA. Saturday. 7 hrs. $90.

November 6—**Four by George Vaillant: Natural History of Male Alcoholism; Hierarchy of Ego Mechanisms; Work as a Predictor of Mental Health; Case Conference.** Del Amo Hospital, Torrance. Saturday. 7 hrs. $50. Contact: Del Amo Hosp. Outreach, 3270 W. Lomita Blvd., Torrance 90505. (213) 872-2482.

November 6-7—**Blood Gas and Acid-Base Disorders.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-7—**Invasive Methods and Hemodynamic Monitoring.** STAN. Saturday-Sunday. 15 hrs. $325.

November 6-7—**Trauma.** STAN. Saturday-Sunday. 11 hrs. $250.

November 6-8—**Nutrition.** PMC and Institute for the Study of Human Knowledge at San Francisco. Saturday-Monday. Contact: PMC.

November 7-12—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui. Sunday-Friday. $350.

November 7-13—**Allergy and Immune Diseases.** Symposium Maui, Inc., and Hawaii Chap., AAFP, at Lahaina Resort, Kaanapali, Maui. One week. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui, HI 96761.

November 10—**Pediatric Emergencies.** LLU. Wednesday. 4 hrs.

November 10—**Nutrition Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

November 10-14—**Sports Medicine Now.** UCD at Hyatt Del Monte, Monterey. Wednesday-Sunday. 24 hrs. $275.

November 11-13—**Critical Decisions in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Thursday-Saturday. 12 hrs. $235. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049, Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 11-13—**First National Conference on Infantile Apnea and Home Monitoring of High Risk Infants.** Eisenhower Medical Center and Medical Center of Tarzana at Eisenhower Med. Ctr., Rancho Mirage. Thursday-Saturday. Contact: Annenberg Center for Health Sciences, Eisenhower Med. Ctr., 39000 Bob Hope Dr., Rancho Mirage 92270. (714) 340-3911, ext. 1661.

November 11-14—**Controversial Areas in Surgery of the Head and Neck.** Institute for Medical Education and Research at Hilton Beach and Tennis Resort, San Diego. 20 hrs. $250. Contact: IMER, P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 11-14—**Allergy/Immunology: Practical Aspects Today and Into the 21st Century.** American Assn. for Clinical Immunology and Allergy at Marriott, Anaheim. Thursday-Sunday. 30 hrs. $250. Contact: Howard S. Silber, Exec. Dir., AACIA, P.O. Box 912-DTS Omaha NE 68101. (402) 551-0801.

November 12-14—**28th Annual Group Therapy Symposium** UCSF at Holiday Inn, Berkeley. Friday-Sunday. 18 hrs $125. Contact: Aveleen Blumenstock, Asst. Dir., Cont. Ed. Langley Porter Institute, 401 Parnassus Ave., Box 2D, San Francisco 94143. (415) 681-8080, ext. 554.

(Continued on Page 16)

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(Continued from Page 14)

November 13—**CT of the Spine.** Cedars-Sinai Medical Center at Century Plaza, Los Angeles. Saturday. 6 hrs. $95. Contact: Kim Reynolds, Cont. Med. Ed., Rm. 2049. Cedars-Sinai Med. Ctr., 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

November 14—**The Lung in 1982.** Granada Hills Community Hospital and UCLA at Sheraton-Universal, North Hollywood. Sunday. Contact: Germaine Trasher, Granada Hills Community Hosp., 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

November 14-17—**California Academy of Family Physicians—Annual Meeting.** Hotel del Coronado Coronado. Sunday-Wednesday. Contact: CAFP, Suite 820, The Hearst Bldg., 5 Third St., San Francisco 94103. (415) 541-0762.

November 15-19—**An International Perspective on Substance Abuse: The Problem, Its Treatment, and Medical Education.** Assn. for Medical Education and Research in Substance Abuse; World Health Org.; State Univ. of NY Downstate Med. Ctr.; et al at Claremont Hotel, Oakland. Monday-Friday. Contact: Dr. Charles Buchwald, Downstate Med. Ctr., 450 Clarkson Ave.-Box 129, Brooklyn, NY 11203. (212) 270-3150.

November 17—**Controversies in the Management of Early Breast Cancer.** Hospital of the Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Institute for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 19-21—**Pain Management.** UCLA. Friday-Sunday.

November 19-22—**Pediatric Update.** Calif. Chapters, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 20-27—**3 for 1: Proctology; Psychiatry; Principles.** Univ. of Washington School of Medicine at Sheraton Waikoloa, Kona, Hawaii. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

November 21-24—**Pacific Coast College Health Association—Annual Meeting.** PCCHA and San Diego State Univ., Student Health Services, at Hyatt Islandia, San Diego. Sunday-Wednesday. 14 hrs. $40, members; $50, nonmembers. Contact: David Bearman, MD, Student Health Services, San Diego State Univ., San Diego 92182. (714) 265-5281.

November 28-30—**Kids Have Bones, Too.** UCD at Hyatt Del Monte, Monterey. Sunday-Tuesday. 11 hrs.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. 2 weeks. 100 hrs. $1,500. Contact: Antonio de la Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 3—**Stroke! An Integrated Approach.** Daniel Freeman Memorial Hospital, Inglewood. Friday. 7 hrs. $90. Contact: Donad A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Mem. Hosp., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

December 3-4—**The Anterior Cruciate Ligament "State of the Art."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 3-4—**Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday-Saturday. 15 hrs.

December 3-5—**Clinical Management of Coronary Disease and Dual-Mode Exercise Testing.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8651.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Fndn. at Hilton Beach Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 4—**Annual Winter Meeting, Emergency Pediatrics, Part II.** Calif. Chapters, American Academy of Pediatrics, at Holiday Inn on Union Square, San Francisco. Saturday. Contact: Beverly Busher, No. Calif. Chap., AAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Ed., Los Angeles 90024. (213) 825-4617.

December 4—**Total Parenteral Nutrition.** UCLA. Saturday.

December 4-5—**Emerging Frontiers in Medicine: An Update for the Practicing Physician.** The Cypress Foundation and UCSF at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $150. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

December 4-5—**MKSAP VI Review Course.** American College of Physicians and UCLA at UCLA. Saturday-Sunday. 12 hrs. $80. Contact: UCLA.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

December 8—**18th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-10—**MKSAP Review Course.** American College of Physicians and UCD at Hyatt Union Square, San Francisco. Thursday-Friday. Contact: UCD.

December 9-12—**American Academy of Psychoanalysis—26th Winter Meeting.** Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, Admin. Dir., AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

December 10-12—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 13-17—**Postgraduate Institute for Emergency Room Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

December 30-31—**Second Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Thursday-Friday. Contact: Arlene M. Ellis, Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105.

January 6-9—**Anesthesia Update—1983.** UCSD at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Jordan Katz, MD, Dept. of Anesthesia (M-004), UCSD, La Jolla 92093. (714) 453-7500, ext. 3292.

January 9-13—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 10-14—**7th Annual Hawaii Echocardiography Conference.** Honolulu Medical Group at Westin Wailea Hotel, Maui. Monday-Friday. 30 hrs. $495. Contact: Yvonne Brewer, Honolulu Med. Grp., Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

(Continued on Page 42)

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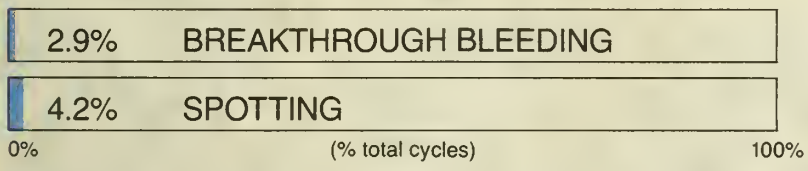
The dosage is lower than "low." Lo/Ovral® contains an "extra-low" total hormone dose—30 mcg ethinyl estradiol and just 0.3 mg norgestrel. Even at this extra-low dose there was no reduction in contraceptive effectiveness. Nor any overall increase in breakthrough bleeding.*

BENEFIT #2: EARLY CYCLE BREAKTHROUGH PROTECTION

Lo/Ovral® offers your patients protection against breakthrough bleeding and spotting when they need it most—in the early cycles.* That's when they're usually most vulnerable to intermenstrual bleeding.

And in clinical trials totalling 22,489 cycles Lo/Ovral achieved a near-spotless record.* Just look below.

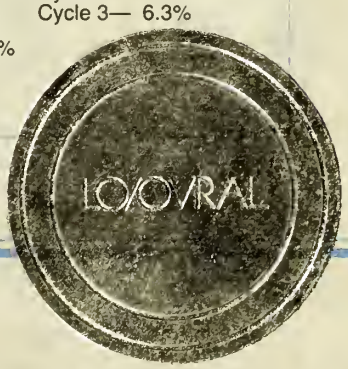


Cycle 1— 8.8%
Cycle 3— 3.3%

Cycle 1—10.6%
Cycle 3— 6.3%

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives.

See full prescribing information.



E IMPORTANT INFORMATION ON FOLLOWING PAGE.

EXTRA-LOW DOSE LO/OVRAL® 30 mcg

each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol, Wyeth.

Oral contraceptive with a near-spotless record.

th Laboratories
Philadelphia, PA 19101

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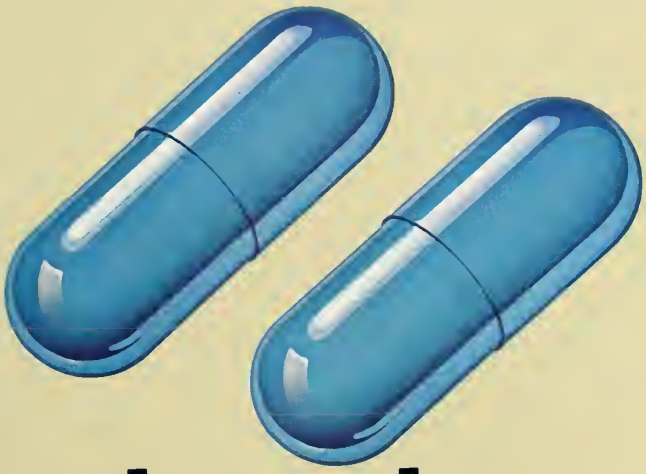
IN BRIEF:
Indications and Usage—LO/OVRAL® is indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.
Contraindications—OC's should not be used in women with any of the following conditions 1 Thrombophlebitis or thromboembolic disorders 2 A past history of deep-vein thrombophlebitis or thromboembolic disorders.
3. Cerebral-vascular or coronary-artery disease
4. Known or suspected carcinoma of the breast.
5. Known or suspected estrogen-dependent neoplasia
6 Undiagnosed abnormal genital bleeding 7 Known or suspected pregnancy (see Warning No. 5) 8 Benign or malignant liver tumor which developed during use of OC's or other estrogen-containing products.
Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems*—An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well established Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause
CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9 5 times greater in users than in nonusers
MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke Furthermore, amount of smoking is also an important factor In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified, quite likely the same synergistic action exists, but perhaps to a lesser extent
RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved This finding has been confirmed in the U S
ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000, ages 35-44—33/100,000, ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs intermittent use Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception Estimates of risk of death for each method include combined risk of contraceptive method (e g , thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure This latter risk varies with effectiveness of method The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of pre-eclamptic toxemia, and especially cigarette smoking. Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g , thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately
A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users
If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.
2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia, papilledema, or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.
3 *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's Of cases found in women without predisposing risk factors (e g irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC These are no longer marketed No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's Several studies have found no increase in breast cancer in women taking OC's or estrogens One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease Reduced occurrence of benign breast tumors in users of OC's has been well documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's Close clinical surveillance of all women on OC's is, nevertheless, essential In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.
4 *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock A few cases of hepatocellular carcinoma have been reported in women on OC's Relationship of these drugs to this type of malignancy is not known.
5 *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare This risk has been estimated to be of the order of 1 in 1,000 exposures or less Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy One case-control study estimated a 4 7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion) Some exposures involved only a few days Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's Embryos with these anomalies are virtually always aborted spontaneously Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive Many clinicians recommend 3 months, although no precise information is available on which to base this The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy
6 *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use In one of the other studies, increased risk was apparent between 6 and 12 months' use
7 *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's For this reason, prediabetic and diabetic patients should be carefully observed while on OC's Increase in triglycerides and total phospholipids has been observed in patients on OC's, clinical significance of this finding remains to be defined.
8 *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year Age is also strongly correlated with development of hypertension in OC users Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug
9 *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC s and evaluation of the cause.
10 *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease. Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities
11 *Ectopic Pregnancy*—Ectopic as well as infrauterine pregnancy may occur in contraceptive failures
12 *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.
Precautions—GENERAL—1 A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination
2 Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.
3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.
4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.
5 Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.
6 Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.
7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.
8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.
9. The pathologist should be advised of OC therapy when relevant specimens are submitted.
10 Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's. a. Increased sulfobromophthalein retention b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; increased norepinephrine-induced platelet aggregability c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d Decreased pregnanediol excretion. e. Reduced response to metyrapone test
Information for the Patient—See Patient Package Labeling
Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone phenytoin sodium, ampicillin and tetracycline.
Carcinogenesis—See Warnings on carcinogenic potential of OC's.
Pregnancy—Category X See Contraindications, Warnings
Nursing Mothers—See Warnings.
Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed. mesenteric thrombosis, neuro-ocular lesions, e g , retinal thrombosis and optic neuritis
The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment, edema; chloasma or melasma which may persist, breast changes: tenderness, enlargement, and secretion, change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice, migraine; increase in size of uterine leiomyomata, rash (allergic); mental depression, reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.
The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted. premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.
Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children Overdosage may cause nausea, and withdrawal bleeding may occur in females

LO/OVRAL® each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.
Wyeth Laboratories, Phila., Pa 19101



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Cephradine for Oral Suspension USP

DESCRIPTION: Velosef '250' Capsules and Velosef '500' Capsules (Cephradine Capsules USP) provide 250 mg and 500 mg cephradine, respectively, per capsule. Velosef Tablets (Cephradine Tablets) provide 1 g cephradine per tablet. Velosef '125' for Oral Suspension and Velosef '250' for Oral Suspension (Cephradine for Oral Suspension USP) after constitution provide 125 and 250 mg cephradine, respectively, per 5 ml teaspoonful.

INDICATIONS AND USAGE: These preparations are indicated for the treatment of infections caused by susceptible strains of designated microorganisms as follows: Respiratory Tract Infections (e.g., tonsillitis, pharyngitis, and lobar pneumonia) due to *S. pneumoniae* (formerly *D. pneumoniae)* and group A beta-hemolytic streptococci [penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever; Velosef (Cephradine, Squibb) is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present]; Otitis Media due to group A beta-hemolytic streptococci, *H. influenzae,* staphylococci, and *S. pneumoniae;* Skin and Skin Structures Infections due to staphylococci and beta-hemolytic streptococci; Urinary Tract Infections, including prostatitis, due to *E. coli, P. mirabilis, Klebsiella* species, and enterococci *(S. faecalis).*

Note: Culture and susceptibility tests should be initiated prior to and during therapy.

CONTRAINDICATIONS: In patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS; *Use cephalosporin derivatives with great caution in penicillin-sensitive patients since there is clinical and laboratory evidence of partial cross-allergenicity of the two groups of antibiotics; there are instances of reactions to both drug classes (including anaphylaxis after parenteral use).* In persons who have demonstrated some form of allergy, particularly to drugs, use antibiotics, including cephradine, cautiously and only when absolutely necessary.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro.* Mild cases of colitis may respond to drug discontinuance alone. Manage moderate to severe cases with fluid, electrolyte and protein supplementation as indicated. Oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis

produced by *C. difficile* when the colitis is severe or is not relieved by drug discontinuance; consider other causes of colitis.

PRECAUTIONS: General: Follow patients carefully to detect any side effects or unusual manifestations of drug idiosyncrasy. If a hypersensitivity reaction occurs, discontinue the drug and treat the patient with the usual agents, e.g., pressor amines, antihistamines, or corticosteroids. Administer cephradine with caution in the presence of markedly impaired renal function. In patients with known or suspected renal impairment, make careful clinical observation and appropriate laboratory studies prior to and during therapy as cephradine accumulates in the serum and tissues. See package insert for information on treatment of patients with impaired renal function. Prescribe cephradine with caution in individuals with a history of gastrointestinal disease, particularly colitis. Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms. Take appropriate measures should superinfection occur during therapy. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Information for Patients: Caution diabetic patients that false results may occur with urine glucose tests (see PRECAUTIONS, Drug/Laboratory Test Interactions). Advise the patient to comply with the full course of therapy even if he begins to feel better and to take a missed dose as soon as possible. Tell the patient he may take this medication with food or milk since G.I. upset may be a factor in compliance with the dosage regimen. The patient should report current use of any medicines and should be cautioned not to take other medications unless the physician knows and approves of their use (see PRECAUTIONS, Drug Interactions).

Laboratory Tests: In patients with known or suspected renal impairment, it is advisable to monitor renal function.

Drug Interactions: When administered concurrently, the following drugs may interact with cephalosporins:

Other antibacterial agents — Bacteriostats may interfere with the bactericidal action of cephalosporins in acute infection; other agents, e.g., aminoglycosides, colistin, polymyxins, vancomycin, may increase the possibility of nephrotoxicity.

Diuretics (potent "loop diuretics," e.g., furosemide and ethacrynic acid) — Enhanced possibility for renal toxicity.

Probenecid — Increased and prolonged blood levels of cephalosporins, resulting in increased risk of nephrotoxicity.

Drug/Laboratory Test Interactions: After treatment with cephradine, a false-positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®. False-positive Coombs test results may occur in newborns whose mothers received a cephalosporin prior to delivery. Cephalosporins have been reported to cause false-positive reactions in tests for urinary proteins which use sulfosalicylic acid, false elevations of urinary 17-ketosteroid values, and prolonged prothrombin times.

Carcinogenesis, Mutagenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential or mutagenesis.

Pregnancy: Teratogenic Effects/Impairment of Fertility — Category B: Reproduction studies have been performed in mice and rats at doses up to 4 times the maximum indicated human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cephradine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.

Nursing Mothers: Since cephradine is excreted in breast milk during lactation, exercise caution when administering cephradine to a nursing woman.

Pediatric Use: Adequate information is unavailable on the efficacy of b.i.d. regimens in children under nine months of age.

ADVERSE REACTIONS: Untoward reactions are limited essentially to G.I. disturbances and, on occasion, to hypersensitivity phenomena. The latter are more likely to occur in persons who have previously demonstrated hypersensitivity and those with a history of allergy, asthma, hay fever, or urticaria.

(continued on next page)

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This offer expires on December 31, 1984.

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(continued)

The following adverse reactions have been reported following use of cephradine: G.I. — Symptoms of pseudomembranous colitis can appear during antibiotic therapy; nausea and vomiting have been reported rarely. Skin and Hypersensitivity Reactions — mild urticaria or skin rash, pruritus, joint pains. Blood — mild transient eosinophilia, leukopenia and neutropenia. Liver — transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage. Renal — transitory rises in BUN have been observed in some patients treated with cephalosporins; their frequency increases in patients over 50 years old. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine. Others — dizziness, tightness in the chest, and candidal vaginitis.

DOSAGE: Adults — For respiratory tract infections (other than lobar pneumonia) and skin and skin structures infections: 250 mg q. 6 h or 500 mg q. 12 h. For lobar pneumonia: 500 mg q. 6 h or 1 g q. 12 h. For uncomplicated urinary tract infections: 500 mg q. 12 h; for more serious UTI, including prostatitis, 500 mg q. 6 h or 1 g q. 12 h. Severe or chronic infections may require larger doses (up to 1 g q. 6 h.).

Children over 9 months of age — 25 to 50 mg/kg/day in equally divided doses q. 6 or 12 h. For otitis media due to *H. influenzae:* 75 to 100 mg/kg/day in equally divided doses q. 6 or 12 h but not to exceed 4 g/day. Dosage for children should not exceed dosage recommended for adults. There are no adequate data available on efficacy of b.i.d. regimens in children under 9 months of age.

For full prescribing information, consult package insert.

HOW SUPPLIED: 250 mg and 500 mg capsules in bottles of 24 and 100 and Unimatic® unit-dose packs of 100. 1 g tablets in bottles of 24. 125 mg and 250 mg for oral suspension in bottles of 100 ml and 200 ml.

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Issued September 1982 782-503

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See next page for brief summary of prescribing information.

Measure RUFEN® (ibuprofen) against "standard" mild to moderate pain

Dental pain and episiotomy pain are predictable, reproducible "standards" that make possible objective comparisons of effectiveness of different analgesic agents.

- Measured against 15, 30 and 60 mg doses of codeine phosphate in a double-blind study of 287 patients, 400-mg doses of ibuprofen proved "significantly better than codeine on almost all pain intensity, degree of relief and duration of analgesia parameters."[2]
- Measured against a propoxyphene-acetaminophen combination for pain relief after 3rd molar extractions, ibuprofen proved equally effective and caused fewer side effects. Ibuprofen was associated with faster recovery, evidenced by more rapid reduction of trismus and return to normal function.[3]
- Measured against post-episiotomy pain in 30 patients, "ibuprofen was effective in treating the swelling as well as pain...during the first and worst days. Therefore, it is not only the analgesic but also the anti-inflammatory effect of ibuprofen that are the beneficial factors..."[4]

Measure RUFEN® (ibuprofen) against any mild to moderate pain

RUFEN	Acetaminophen + codeine combination
• single-entity, peripheral-acting analgesia	• combined drugs act partly through central opioid pathways
• powerful treatment of both pain and inflammation	• virtually no treatment of the inflammatory component
• better tolerated than aspirin	• combined side effects of two drugs—warning required about driving or operating machinery; possible respiratory depression with alcohol, tranquilizers, other common medications
• no narcotic risk, red tape, records	• narcotic precautions required
• matchless economy in a modern NSAID	

References:

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And Rufen® Measures Up Best

RUFEN® (ibuprofen) Tablets

INDICATIONS AND USAGE: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in the long-term management of these diseases. Safety and effectiveness have not been established for Functional Class IV rheumatoid arthritis.

Relief of mild to moderate pain. Treatment of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen, or with the syndrome of nasal polyps, angio-edema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (see WARNINGS).

WARNINGS: Anaphylactoid reactions have occurred in patients hypersensitive to aspirin (see CONTRAINDICATIONS). Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Peptic ulceration, perforation, or gastrointestinal bleeding can end fatally, however, an association has not been established. Rufen should be given under close supervision to patients with a history of upper gastrointestinal tract disease, and only after consulting the ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be attempted. If Rufen must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If developed, discontinue Rufen and administer an ophthalmologic examination.

Fluid retention and edema have been associated with Rufen; caution should be used in patients with a history of cardiac decompensation.

Rufen can inhibit platelet aggregation and prolong bleeding time. Use with caution in patients with intrinsic coagulation defects and those taking anticoagulants.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy, this therapy should be tapered slowly when adding Rufen.

DRUG INTERACTION: *Coumarin-type anticoagulants*. The physician should be cautious when administering Rufen to patients on anticoagulants.

Aspirin. Concomitant use may decrease Rufen blood levels.

PREGNANCY AND NURSING MOTHERS: Rufen should not be taken during pregnancy nor by nursing mothers.

ADVERSE REACTIONS: Incidence greater than 1%. Gastrointestinal: The most frequent adverse reaction is gastrointestinal (4 to 16%). Includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distre nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence). Central Nervous System: dizziness*, headache, nervousness. Dermatologic: rash* (including maculopapular type), pruritus. Special Senses: tinnitus. Metabolic: decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS). *Incidence 3% to 9%

Incidence less than 1 in 100. Gastrointestinal: gastric or duodenal ulcer with bleeding and/or perforation, hemorrhage, melena. Central Nervous System: depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma. Dermatologic: vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome and alopecia. *Special Senses*: hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) [see PRECAUTIONS]. Hematologic: neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs' positive), thrombocytopenia with or without purpura eosinophilia, decreases in hemoglobin and hematocrit. Cardiovascular: congestive heart failure in patients with marginal cardiac function, elevated blood pressure. Allergi syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasms (see CONTRAINDICATIONS). Renal: acute renal failure in patients with preexisting significantly impaired renal function decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria. Miscellaneous: dry eyes and mouth, gingival ulcers, rhinitis.

Causal relationship unknown. Gastrointestinal: pancreatitis. Central Nervous System: paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri. Dermatologic: toxic epidermal necrolysis, photoallergic skin reactions. Special Senses: conjunctivitis, diplopia, optic neuritis. Hematologic: bleeding episodes. Allergic: serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis. Endocrine: gynecomastia, hypoglycemia. Cardiovascular: arrhythmias (sinus tachycardia, bradycardia, and palpitations). Renal: renal papillary necrosis.

OVERDOSAGE: Acute overdosage, the stomach should be emptied. Rufen is acidic and excreted in the urine, alkaline diuresis may benefit.

DOSAGE AND ADMINISTRATION: Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease: Suggested dosage 400 mg t.i.d. or q.i.d.

Dysmenorrhea: 400 mg every 4 hours as necessary.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain. *Do not exceed 2,400 mg per day*

CAUTION: Federal law prohibits dispensing without prescription.

Ativan®: (lorazepam) Agent of Change because...

shorter acting, less accumulation

Unlike most benzodiazepines, Ativan has a short half-life, no active metabolites, and accumulation to steady state extends for only 2-3 days. Ativan is therefore less likely to cause excessive sedation.*

no interaction with drugs metabolized by P450 enzymes

Because it is metabolized by simple conjugation rather than complex oxidative reactions, Ativan does not compete with other drugs for hepatic P450 microsomal enzymes. Concomitant use with Tagamet® (cimetidine), for example, does not result in delayed clearance or increased sedation†—effects which have been reported with other benzodiazepines.[1-5]

greater control of therapy

The short half-life of Ativan facilitates more rapid response to dosage adjustments, aiding you in titrating therapy to the patient's changing needs. Once you decide to discontinue Ativan, it will be out of your patient's system 4 days after the final dose—unlike the long-acting, multi-metabolite benzodiazepines which take as long as 2 weeks to be totally eliminated.

Wyeth Laboratories
Philadelphia, PA 19101

References:
1. Klotz U, Reimann I. N Engl J Med *302*:1012-1014, 1980
2. Desmond PV, Patwardhan RV, Schenker S, et al: Ann Intern Med *93* 266-268, 1980.
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*Pharmacokinetics cannot as yet be directly related to efficacy
All benzodiazepines produce additive effects when given with CNS depressants such as barbiturates or alcohol.

See important information on following page.

Ativan® for (lorazepam)® Anxiety

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence. Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan®
for (lorazepam)
Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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BECAUSE
A THIAZIDE ALONE
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INCREASE CONTROL WITHOUT INCREASING POTASSIUM PROBLEMS.

A dependable means to long-term blood pressure control.

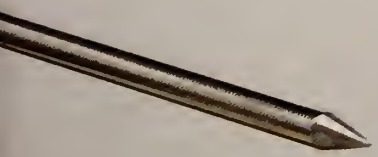
Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.



INDERIDE®

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

When you know you need more than a thiazide.

Please see Brief Summary of Prescribing Information on following page.

INDERIDE®

Each tablet contains INDERAL (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

NEW TABLET SHAPE ™

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

INDERIDE®
BRAND OF
propranolol hydrochloride (INDERAL®)
and hydrochlorothiazide

No. 484—Each INDERIDE® 40/25 tablet contains	
Propranolol hydrochloride (INDERAL®)	40 mg
Hydrochlorothiazide	25 mg
No. 488—Each INDERIDE®-80/25 tablet contains	
Propranolol hydrochloride (INDERAL®)	80 mg
Hydrochlorothiazide	25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATION: INDERIDE is indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma, 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock, 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol, 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, e.g., isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (e.g., CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers. Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular:* bradycardia, congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type, thrombocytopenic purpura.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpur

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal:* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic react

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: —Each hexagonal-shaped, off-white, scored INDERIDE 40/25 tablet is embossed with an "I" and imprinted with "INDERIDE 40/25," contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0484-81) and 1,000 (NDC 0046-0484-91). Also in unit dose package of 100 (NDC 0046-0484-99).

—Each hexagonal-shaped, off-white, scored INDERIDE 80/25 tablet is embossed with an "I" and imprinted with "INDERIDE 80/25," contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0488-81) and 1,00 (NDC 0046-0488-91). Also in unit dose package of 100 (NDC 0046-0488-99).

The appearance of these tablets is a trademark of Ayerst Laboratories.

Store at room temperature (approximately 25° C).

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A NEW AGE IN THE CONTROL OF ANGINA

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PROCARDIA®

(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:

—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply

—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand

—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

PROCARDIA®

THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page.

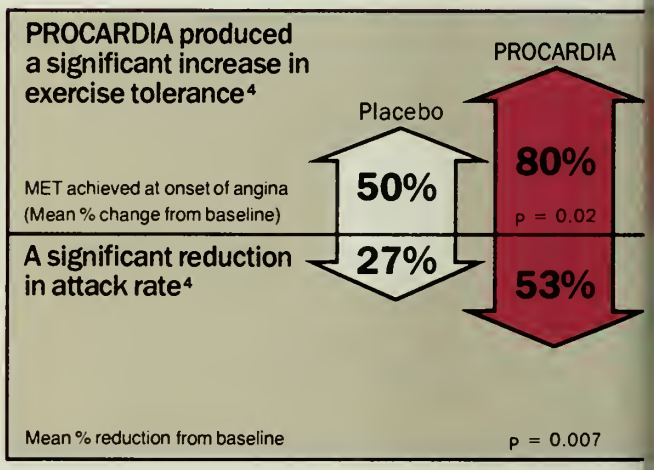
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional therapy



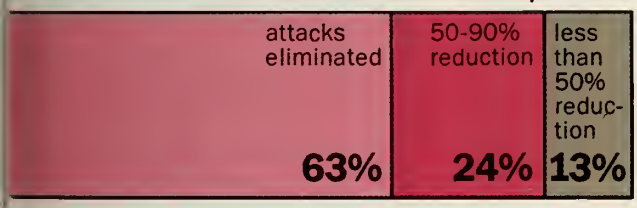
Double-blind, placebo-controlled, crossover 20-week study of 32 patients (27 evaluated for attack rate; 19 for exercise tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete

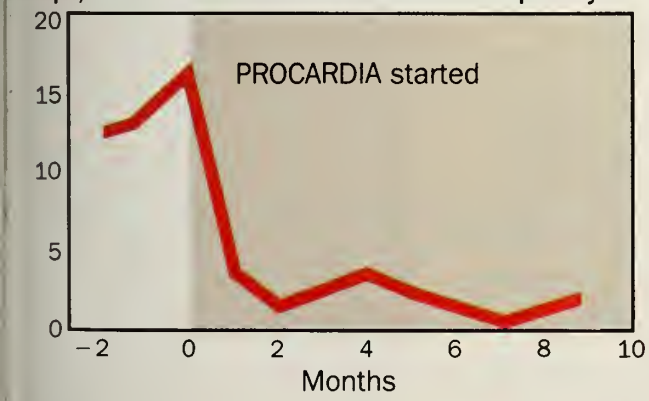
Please see PROCARDIA Brief Summary on last page

ı vasospastic angina

ROCARDIA eliminated attacks in 63% of patients[5]

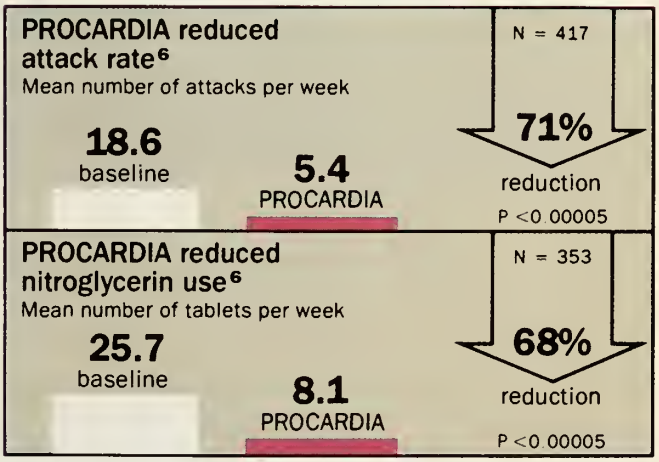


rompt, sustained decrease in attack frequency[5]



ıng-term, open study of 127 patients unresponsive to beta ockers and/or nitrates with symptoms of myocardial chemia and demonstrated coronary artery spasm. ROCARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)



Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

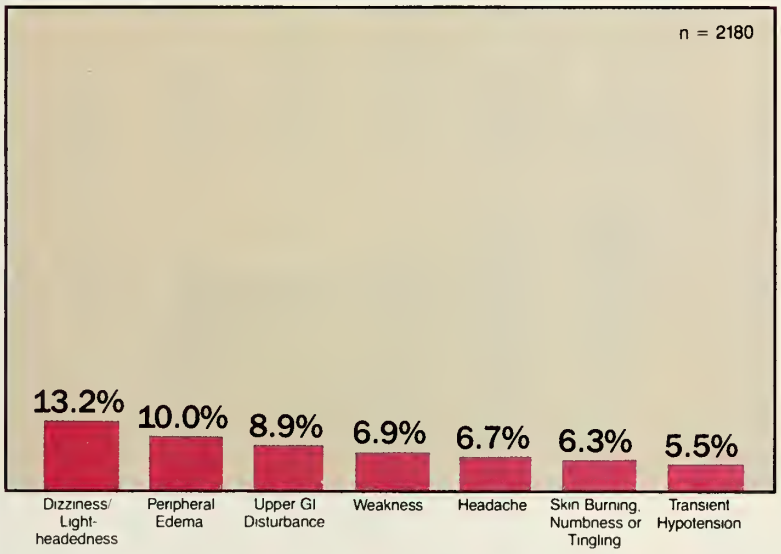
—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

Please see PROCARDIA Brief Summary on last page.

THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

Most common adverse reactions



Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

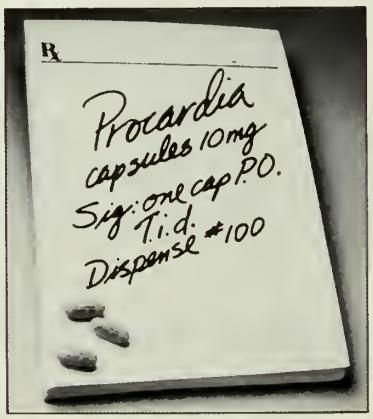
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

References

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2. Maseri A, Chierchia S. Angina pectoris—a new dimension, a new approach. Part 2. *Primary Cardiol* 6:123–136, October 1980.
3. Braunwald E. *Introduction: New Concepts in Ischemic Heart Disease: The Role of Coronary Artery Spasm.* New York, Science & Medicine, Inc, 1980, p 1.
4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302:1269–1273, June 5, 1980.
6. Braunwald E (moderator). Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, April 29, 1982.

PROCARDIA® CAPSULES For Ora

(nifedipine)

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedi
indicated for the management of vasospastic angina confirmed by any of the fo
criteria: 1) classical pattern of angina at rest accompanied by ST segment ele
2) angina or coronary artery spasm provoked by ergonovine, or 3) angiogra
demonstrated coronary artery spasm. In those patients who have had angio
the presence of significant fixed obstructive disease is not incompatible v
diagnosis of vasospastic angina, provided that the above criteria are sa
PROCARDIA may also be used where the clinical presentation suggests a
vasospastic component but where vasospasm has not been confirmed, e.g.
pain has a variable threshold on exertion or in unstable angina where elect
ographic findings are compatible with intermittent vasospasm, or when a
refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROC
is indicated for the management of chronic stable angina (effort-associated
without evidence of vasospasm in patients who remain symptomatic despi
quate doses of beta blockers and/or organic nitrates or who cannot tolerat
agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been e
in controlled trials of up to eight weeks duration in reducing angina frequer
increasing exercise tolerance, but confirmation of sustained effectiveness a
uation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant
PROCARDIA and beta-blocking agents may be beneficial in patients with
stable angina, but available information is not sufficient to predict with confide
effects of concurrent treatment, especially in patients with compromised left
ular function or cardiac conduction abnormalities. When introducing such conc
therapy, care must be taken to monitor blood pressure closely since severe h
sion can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypo
effect of PROCARDIA is modest and well tolerated, occasional patients h
excessive and poorly tolerated hypotension. These responses have usually o
during initial titration or at the time of subsequent upward dosage adjustme
may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have de
well documented increased frequency, duration or severity of angina on
PROCARDIA or at the time of dosage increases. The mechanism of this resp
not established but could result from decreased coronary perfusion associa
decreased diastolic pressure with increased heart rate, or from increased
resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdra
drome with increased angina, probably related to increased sensitivity to c
amines. Initiation of PROCARDIA treatment will not prevent this occurre
might be expected to exacerbate it by provoking reflex catecholamine releas
have been occasional reports of increased angina in a setting of beta block
drawal and PROCARDIA initiation. It is important to taper beta blockers if p
rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta block
developed heart failure after beginning PROCARDIA. Patients with tight a
nosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases
eral vascular resistance, careful monitoring of blood pressure during the initia
istration and titration of PROCARDIA is suggested. Close observation is e
recommended for patients already taking medications that are known to low
pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associa
arterial vasodilation and not due to left ventricular dysfunction, occurs in abou
ten patients treated with PROCARDIA. This edema occurs primarily in th
extremities and usually responds to diuretic therapy. With patients whose a
complicated by congestive heart failure, care should be taken to different
peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications an
ings.) Experience in over 1400 patients in a non-comparative clinical trial ha
that concomitant administration of PROCARDIA and beta-blocking agents is
well tolerated, but there have been occasional literature reports suggesting
combination may increase the likelihood of congestive heart failure, severe h
sion or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with
but there have been no controlled studies to evaluate the antianginal effectiv
this combination.

Pregnancy: Category C

ADVERSE REACTIONS: The most common adverse events include dizz
light-headedness, peripheral edema, nausea, weakness, headache and
each occurring in about 10% of patients, transient hypotension in about 5%,
tion in about 2% and syncope in about 0.5%. Syncopal episodes did not re
reduction in the dose of PROCARDIA or concomitant antianginal medicati
rarely, introduction of PROCARDIA therapy was associated with an increas
ginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily disting
from the natural history of the disease in these patients. It remains possible,
that some or many of these events were drug related. Myocardial infarction
in about 4% of patients and congestive heart failure or pulmonary edema
2%. Ventricular arrhythmias or conduction disturbances each occurred in fe
0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzym
as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been note
single incident of significantly elevated transaminases and alkaline phosphat
seen in a patient with a history of gall bladder disease after about eleven m
nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. Th
oratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contain
of nifedipine. PROCARDIA Capsules are supplied in amber glass bottle
capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at c
room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original co

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In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis and of impotence have been reported with the use of 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Package (unit-dose) of 100 (intended for institutional use only); Patient-Pak™ unit-of-use bottles of 100.

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THE WESTERN
Journal of Medicine

Refer to: Berek JS, Hacker NF, Lagasse LD: Recent progress in the treatment of epithelial ovarian malignancy. West J Med 1982 Oct; 137:273-277

Recent Progress in the Treatment of Epithelial Ovarian Malignancy

JONATHAN S. BEREK, MD; NEVILLE F. HACKER, MD, *and*
LEO D. LAGASSE, MD, *Los Angeles*

Improved surgical and chemotherapeutic management has ensured that more than half the patients with advanced ovarian cancer will be clinically free of disease shortly after treatment begins. Aggressive cytoreductive surgical treatment and combination cytotoxic chemotherapy have appreciably prolonged survival and have induced cures in some women with metastatic disease. An increasing number of women are being seen with small residual disease at second-look laparotomy, and intraperitoneal administration of chemotherapeutic and immunotherapeutic agents is being investigated for these patients. Specific immunotherapies, including monoclonal antibodies raised against patients' own tumor cells, are also being investigated. During the next five years we may see significant improvement in the cure rate for this disease.

Of all the diseases unique to women, malignant disease of the ovary is a foremost cause of death in the United States. Over 11,400 women succumbed to ovarian cancer in 1981.[1] According to some estimates, this disease develops in 1 of every 70 women in the United States.[2]

Epidemiologic studies have failed to identify any consistent predisposing factors associated with the disease. The increased prevalence of ovarian cancer in single women, however, including nuns and nulliparous married women, suggests that incessant ovulation uninterrupted by pregnancy may be a predisposing factor.[3]

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, UCLA School of Medicine and The Center for Ovarian Cancer of the Jonsson Comprehensive Cancer Center, Los Angeles.

Submitted March 8, 1982.

Reprint requests to: Jonathan S. Berek, MD, Division of Gynecologic Oncology, UCLA School of Medicine, Los Angeles, CA 90024.

Unfortunately, in more than 70 percent of cases, ovarian carcinoma has metastasized by the time it is diagnosed.[4] Diagnosis is usually suspected after detection of a pelvic or abdominal mass on clinical examination, and confirmed at exploratory laparotomy. This is because ovarian carcinoma tends to be asymptomatic until the disease is advanced, and no sensitive screening test is available to asymptomatic women.

Transcoelomic spread is the most common form of dissemination, with metastasis commonly occurring in the omentum, paracolic gutters and undersurface of the diaphragm. Lymphatic dissemination also occurs early in the course of the disease, with pelvic and periaortic lymph nodes frequently involved. With more advanced disease, lymphatic channels in the diaphragm become blocked, resulting in clinically evident ascites.

Metastasis via blood vessels rarely occurs, so most patients with advanced disease do not have spread outside the abdominal cavity.

Treatment

Chemotherapy

Chemotherapy has been the primary therapy for advanced ovarian malignancy. Whereas single alkylating agents were the treatment of choice for many years, multiagent combination chemotherapy is now becoming the standard treatment. Agents such as cisplatin, doxorubicin hydrochloride, cyclophosphamide, hexamethylmelamine and vinblastine sulfate have shown activity against these tumors. Recent reports indicate that response rates of about 70 percent to 80 percent may be expected in patients with stages III and IV disease. Approximately half of these patients will have complete clinical responses. Such patients have been reported to have actuarial survival rates of greater than 50 percent at three years.[5] More complete responses to chemotherapy have been seen in patients who have had optimal tumor cytoreduction before beginning their therapy.[5,6] In addition, it has been shown that combination chemotherapy is better than single alkylating agents only when used in patients who have undergone optimal cytoreductive surgical treatment.[5]

Surgical Procedures

Several studies have indicated the value of reducing the tumor burden at the start of chemotherapy.[6,7] When the size of the largest residual tumor at the beginning of chemotherapy is less than 1.5 to 2 cm, patients have been shown to have a longer median survival, independent of tumor grade. These reports have prompted many gynecologic oncologists to do an initial cytoreductive surgical procedure in a further attempt to prolong life and achieve a cure following multiagent chemotherapy.

Our approach has been to do cytoreductive operations in all cases with a primary diagnosis of ovarian cancer, and occasionally in cases with a primary diagnosis of recurrent or persistent disease. The operation typically consists of a total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, resection of paracolic and peritoneal tumors, selective lymphadenectomy and occasionally bowel or lower urinary tract resection. In our experience, optimal surgical cytoreduction (that is, the largest residual mass being 1.5 cm in diameter) can be accomplished in about two thirds of patients with advanced disease (stages III and IV).[8]

Our results indicate that the amount of residual disease following surgical intervention, the presence of clinical ascites and the diameter of the largest metastatic lesion significantly affect survival. Patients with residual tumor of 5 mm or less in diameter had a median survival of 40 months, compared with 18 months for those with residual disease between 5 and 15 mm and six months for those with a residual mass larger than 15 mm ($P<.001$). For patients whose tumors could be optimally cytoreduced, those without clinical ascites had a median survival of 32 months compared with 12 months for those with ascites ($P<.03$). For those whose largest metastatic disease was 10 cm or smaller before optimal cytoreduction, the median survival was 36 months compared with 12 months for those with metastatic disease larger than 10 cm ($P<.01$). The survival was independent of patient age, tumor grade, the type of chemotherapy and the diameter of the primary lesion.

In spite of these strong retrospective analyses, many physicians do not believe in the value of tumor cytoreduction in patients with epithelial ovarian malignancy. A randomized prospective study is necessary to address this issue, but until the results of such a study are available, we feel that, in view of the proved low morbidity associated with aggressive primary cytoreduction, it should be the standard of care for patients with advanced ovarian cancer.

In patients with no gross evidence of disease outside the pelvis (stages I and II), a thorough staging procedure is undertaken to rule out occult dissemination. A staging laparotomy includes doing an omentectomy, selective lymphadenectomy, multiple intraperitoneal biopsies and a peritoneal cytologic examination.

Operative procedures required for cytoreduction of ovarian cancer are not uniformly understood. Despite misconceptions to the contrary, tumor masses can usually be removed without being transected because lines of cleavage between tumor-bearing peritoneum and normal tissue are usually found. Omentectomy is carried out by ligating the gastroepiploic vessels along the greater curvature of the stomach, exposing the lesser sac and transverse mesocolon.[7] Although bowel or lower urinary tract resections are occasionally necessary, tumor implants can usually be removed

from the bowel or bladder serosa by sharp dissection.[9,10] Excision of all gross tumor in the pelvis is facilitated by a retroperitoneal dissection along the iliac vessels and ureters from the pelvic brim to the lower limit of tumor growth.

Radiation Therapy

The role of radiation therapy for patients with ovarian cancer is being redefined. Dembo and co-workers[11] prospectively evaluated the use of whole abdomen irradiation in patients, most of whom (86 percent) had disease confined to the pelvis (stages IB and II); they achieved a 78 percent five-year actuarial relapse-free survival. They used the so-called moving-strip technique for abdominopelvic irradiation and extended the upper limits of the field to 1 cm above the diaphragm. Their results were better than any previously reported, an improvement they attributed to adequate irradiation of the diaphragm, a frequent site of occult disease. Whole abdomen irradiation is now being more widely evaluated in the hope of more precisely defining the patient population most likely to benefit from this mode of therapy. For early stage disease that can be completely resected, radiocolloids such as radioactive phosphorus (^{32}P) and gold (^{198}Au) have been used and have been reported to augment survival in such patients.[12]

We have used whole abdomen irradiation as "second-line" treatment in some patients with incomplete responses to primary chemotherapy, and in whom there is little residual disease. Bone marrow intolerance is sometimes a problem, but we have been encouraged by the initial results in patients able to tolerate the therapy without significant treatment delays.

Second-Look Operations

Following a course of chemotherapy, typically consisting of 8 to 12 cycles, a second-look laparotomy is done if a patient is clinically free of disease. If any gross disease is present, an attempt is made to resect as much of it as possible before the institution of second-line therapy. If no gross tumor is present, a thorough inspection of all the intraabdominal viscera is made, multiple peritoneal washings are done for cytologic study and multiple biopsy specimens are taken from peritoneal surfaces and retroperitoneal lymph nodes. Recently it has become apparent that prolonged use of alkylating agents is associated with a significantly increased risk of acute nonlymphocytic leukemia developing; hence, prolonged therapy is unwise.[13] In about 30 percent to 40 percent of patients in clinical remission, findings will be negative on second-look laparotomies, thus permitting discontinuing their chemotherapy. About 75 percent of patients with negative findings on a second laparotomy will survive five years without clinical evidence of recurrence.[14]

It has also been suggested that laparoscopy (peritoneoscopy) may be useful in monitoring response to chemotherapy. Serial laparoscopies may be carried out on patients in clinical remission (for example, at four- to six-month intervals), thus allowing subclinical progression of disease to be detected at the earliest possible time so that alternative therapies may be instituted.[15]

At the time of a secondary operation for patients with ovarian cancer, either at "second look" or to assess clinical progression, the question arises as to whether or not persistent tumor should be resected. Based on a recent review of our clinical experience in 32 patients, we found optimal secondary resection of tumor was associated with a significantly longer median survival.[16] The feasibility of optimal resection, however, was only 38 percent, compared with 66 percent for patients who underwent primary tumor debulking. The median survival of patients who had an optimal secondary cytoreductive operation was 20 months compared with only five months for the nonoptimal group ($P<.01$). Patients who had clinically inapparent ascites fared much better than those with gross ascites (18 versus 5 months) ($P<.01$). Patients with smaller tumors (5 cm or less in maximum diameter) before resection had a median survival of 20 months, compared with only six months in those with larger tumors ($P<.01$). Patient age, tumor grade, the type of chemotherapy and the presence of bowel obstruction per se did not influence the subsequent survival. Thus, for patients who have incomplete responses to chemotherapy and have tumor discovered at second look, an attempt should be made to resect the residual disease. Furthermore, patients with clinical progression, if without ascites, may also benefit from tumor resection if feasible.

Prospects for the Future

With aggressive primary surgical treatment and multiagent chemotherapy, an increasing number of patients is being seen with complete clinical responses and minimal residual disease at second-look laparotomies. Our major research efforts are

now being directed toward the development of effective second-line therapies for this group of patients.

Intraperitoneal Chemotherapy

A major new development is the intraperitoneal administration of chemotherapy. Our group is studying the feasibility and toxicity of the intraperitoneal administration of cisplatin in women with persistent or recurrent carcinoma confined to the peritoneal cavity. Current data derived from studies with animals done at UCLA have shown that following intraperitoneal administration of cisplatin, drug concentrations in tissues lining the peritoneal cavity are 2½ to 8 times higher than following intravenous administration of the same dose of the drug.[17] Because ovarian cancer implants on peritoneal surfaces, intraperitoneal administration should result in maximal drug concentration in the tumor. The drug is administered through an indwelling intraperitoneal (Tenckhoff) catheter, and we have found this therapy to be well tolerated by patients. Because the drug does not remain in the peritoneal cavity for long, systemic absorption and toxicity are decreased.[18]

Intraperitoneal Immunotherapy

Immunotherapy has been most effective in animals when tumor burdens are small and immunologic agents can be brought into direct contact with tumor cells.[19] Hence, intraperitoneal immunotherapy might be expected to significantly prolong survival in ovarian cancer patients by eliminating the small number of tumor cells that remain following administration of chemotherapy.

Corynebacterium parvum has exerted antitumor activity in a variety of animals. From a recent review of other articles, *C parvum* appears to offer advantages over some other immunostimulants, particularly because of its effect on natural-killer lymphocyte and macrophage function, the stimulation of which seems important for tumor cell destruction in the peritoneal cavity.[19]

A collaborative phase I trial of intraperitoneally administered *C parvum* is under way at UCLA and the Sidney Farber Cancer Center in Boston. Thus far, 12 patients have received therapy and five have responded, three with complete surgical responses.

Hormone Receptors

The role of estrogen and progesterone receptors in neoplastic tissues has been extensively studied in breast cancer, but the technology has only recently been applied to the assessment of the female genital tract. In our laboratories, we have preliminary data that have suggested for the first time that levels of estrogen and progesterone receptors can be correlated with the histologic type and tumor grade of the ovarian carcinomas.[20] This implies that a more rational approach can be developed for the clinical use of antiestrogen and progestational agents for the treatment of advanced ovarian cancer.

Clonogenic Assay

The tumor colony, "clonogenic" assay, is now being used to determine the in vitro sensitivity to various chemotherapeutic agents before beginning therapy for ovarian cancer. The test helps to individualize the treatment, especially by excluding those drugs without apparent efficacy. If the test shows absence of in vitro sensitivity, the clinical response rate is less than 10 percent whereas positive sensitivities correlate with clinical responses in about 40 percent to 50 percent of patients.[21]

Monoclonal Antibodies

The pioneering work of Köhler and Milstein[22] has accomplished a potentially giant step in immunotherapy technology. Mouse myeloma cells were successfully fused with lymphocytes from the spleen of mice immunized with a particular antigen. The product was a hybrid myeloma cell, a so-called hybridoma. These new hybrid cells could express the lymphocyte's property of specific antibody production. Individual hybrid cells can be cloned and each clone can thus produce large quantities of identical antibody to a single antigenic determinant.

Monoclonal antibodies can be raised against antigenic determinants on human ovarian cell lines.[23] Furthermore, the method may potentially be applied to the serologic diagnosis, and the treatment of ovarian cancer. Research is currently being done to develop monoclonal antibodies in patients with ovarian cancer in an effort to establish a technique for early detection and monitoring of the disease. These antibodies may also prove to have some therapeutic value in ovarian cancer, particularly in patients with small residual disease.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Challenge Food Testing for Rheumatoid Arthritis

QUESTION:

Is it accepted medical practice to perform diagnostic evaluation of food allergy as a cause of rheumatoid arthritis?

If yes, is it accepted practice to hospitalize the patient for a 96-hour fast followed by reintroduction of foods into the diet one at a time to observe symptoms? Are other diagnostic methods accepted for evaluation of food allergy as a cause of rheumatoid arthritis?

OPINION:

In the opinion of the Advisory Panels on Allergy, Internal Medicine and Orthopedics, it is not accepted medical practice to perform diagnostic evaluation of food allergy as a cause of rheumatoid arthritis. There is no established scientific information or theoretical basis for considering food allergy as a cause or contributing factor to this disease.

Some panelists noted that the evaluation of food allergy in rheumatoid arthritis could be the subject of investigation under a well-planned research protocol. The use of a 96-hour fast in hospital, followed by reintroduction of foods, would be unnecessary for most investigators. Simple elimination diets on an outpatient basis and double-blind challenges are acceptable medical procedures to make the diagnosis of food allergy.

Refer to: Moore BC, Glover TW, Kaiser-McCaw B, et al: Fragile X-linked mental retardation and macro-orchidism. West J Med 1982 Oct; 137:278-281

Fragile X-Linked Mental Retardation and Macro-orchidism

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A fragile site near the end of the long arm (q) of the X chromosome appears to be directly related to the gene responsible for the mental retardation found among males and some females who possess this variant X chromosome. Macro-orchidism is present in most males studied. Other mild phenotypic similarities may exist. The expression of the fragile X (fra[X]) chromosome is dependent on the concentration of folic acid and thymidine in the culture medium, which partly explains why fra(X) was not noted earlier and connected promptly with X-linked mental retardation. Whereas prenatal diagnosis is now possible, genetic counseling is complicated by recent reports of "intellectually normal" fra(X) males. Further studies are needed to form solid conclusions about intellectual deficits, learning behavior or personality characteristics of fra(X) persons.

THE LIST OF chromosome aberrations related to human pathologic conditions has grown rapidly during recent years, but research has seldom found conditions that were individually frequent, predictably heritable or potentially preventable. A major new chromosome abnormality, however, has been found associated with X-linked mental retardation. This chromosome abnormality is the fragile X (fra[X]). The prospect that fragile X research may lead to the discovery of a relatively common mental retardation syndrome and that it has been identified prenatally through amniocentesis[1,2] is stirring great interest. The possibility of amelioration or prevention through treatment[3] adds fascination to fragile X chromosome studies.

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History

The history of fragile X chromosome research began with the observation that there is significantly more retardation among men than women. Later pedigrees were recorded showing that at least some of the excessive retardation among males could be explained through X linkage.[4-8] In most cases, however, no clearly defined syndrome or biochemical abnormality could be determined and the term *nonspecific X-linked mental retardation* was used to describe these conditions. It is now clear that nonspecific X-linked mental retardation represents a heterogeneous group of dis-

orders, but that a major subgroup, representing perhaps 30 percent of such families,[9] is associated with the fragile X chromosome.

The first fragile X chromosome report was made by Lubs[10] in 1968, but its significance was not generally appreciated at that time. Confirmation of this aberration was later provided by Giraud, Ayme, Mattei and co-workers[11] in 1976 and Harvey, Judge and Wiener[12] in 1977. The reason for such a sparse sighting record was provided by Sutherland in a series of reports.[13-15] He found that the expression of the fragile site on the X chromosome was inhibited by the presence of folic acid and thymidine in the culture medium; in fact, the percentage of cells with the fragile X chromosome observed in cultures increased when the amount of folic acid was decreased.

In experiments to understand the nature of folic acid inhibition, Glover[16] and Tommerup and colleagues[17] found that the fra(X) is induced by floxuridine (2′-deoxy-5-fluorouridine), a potent inhibitor of the enzyme thymidylate synthetase. These observations lead to the suggestion that the fragile site is seen due to specific limitation of thymidine 5′-phosphate available for DNA synthesis. Knowledge that special culture conditions are required for observation of the fragile X opened the way for diagnosis and further research.

Characteristics

The fragile X chromosome (See Figure 1), also called marker X (mar[X]),[10,18,19] is a variant X chromosome with a gap or fragile site at the distal end of the long arm at Xq28, resulting in the appearance of an X chromosome with a "satellite." (There is some confusion about the exact location of Xq, and some researchers refer to the site as Xq27.) Under normal culture conditions the gap is not seen. Even under optimal conditions, the fragile site is usually seen in less than half of all metaphases from affected males and may not be seen at all in cultured lymphocytes from certain carrier females, causing considerable difficulty in carrier detection and genetic counseling. Jacobs, Glover, Mayer and associates[20] have found the proportion of cells showing the fragile X chromosome in females to be positively correlated with lowered mental ability and inversely correlated with age. All early observations of the fragile X chromosome were in cultured lymphocytes. Recent inductions of the fragile X chromosomes in cultured fibroblasts[16,17,21] have led to procedures for diagnosis of the fragile X in amniocytes.[1,2]

In 1965 Dekaban[22] first described what were later to be called *fragile sites* in human chromosomes. Subsequently, fragile sites have been observed on chromosomes 2, 6, 7, 9 through 12, 16, 20 and the X. As yet, only the X fragile site has been clearly associated with human pathologic disorders.

It is evident that the fragile X chromosome is associated with mental retardation in males. Whereas Hecht and Kaiser-McCaw[23] noted that it has not yet been determined whether the variant

Figure 1—The two X chromosomes from a female carrier of the fragile X. **Left,** unbanded; **right,** the same chromosomes G-banded. The fragile site gives the appearance of "satellites" on the distal end of the long arm of the X chromosome.

fragile X site actually causes mental retardation or is closely linked to a mental retardation gene, the same investigators later point out that no single instance of crossing over between the fragile X and mental retardation had been fully reported. It is their view that the fragile site on the X chromosome may be a cytologic reflection of the gene responsible for concomitant mental retardation.[24]

Macro-orchidism also has been associated with the fragile X site.[6,9,18,19,25-29] The presence of macro-orchidism appears to be a strong phenotypic indicator of the presence of fra(X) and mental retardation, though some affected males have testes of normal size. For example, Turner and co-workers[28] reported that 24 of 25 males with fra(X) had testicular enlargement and Jacobs and associates[20] found 22 of 24 fra(X) men to have large testes. Lack of precision in measuring the testes, difficulties associated with prepubertal determination of adult testicular dimensions and the as-yet-unresolved laboratory problems with regard to the Xq fragile site may all have contributed to blurring relationships among fra(X), mental retardation and macro-orchidism. Howard-Peebles and Stoddard[25] have noted that physicians may not accurately observe macro-orchidism at times and therefore recommended the use of an orchidometer to improve evaluations.

Research has not yet established whether a consistent pattern of phenotypic abnormality other than macro-orchidism is present in fra(X) males. Of the four persons discussed by Lubs,[10] one had no congenital anomalies, one had a "stiff-legged gait" but otherwise no abnormalities and one had a prominent maxilla, large low-set ears, cogwheeling arm movements and rigidity. The fourth person had microcephalia and slight spasticity. Harvey and colleagues[12] described fra(X) males from four families as being "essentially phenotypically normal." After reviewing 25 fra(X) male subjects, however, Turner and associates[28] reported that whereas the facial appearance of these persons was essentially normal, there was a suggestion of certain features in common: a larger than normal forehead with supraorbital fullness, prominent chin, large ears and a predominance of pale blue irides. Turleau, Czernichow, Gorin and co-workers[29] reported the case of a 13-year-old with mental retardation, macro-orchidism and "peculiar facies" reminiscent of that seen with trisomy 8. Jacobs and associates[20] observed six families; fragile X males in this study shared characteristic facial changes (that is, large ears and prominent jaw). These investigators concluded, however, that the changes were not pathognomonic as they occur commonly in normal populations. Because most other researchers have looked at relatively small numbers of fra(X) persons, usually siblings or otherwise related, the phenotypic resemblance noted by Turner and colleagues[28] may have gone unnoticed, or have been judged to be a familial resemblance. Additional data on large numbers of fra(X) male subjects doubtless will be required before questions of phenotype can be clarified.

Questions of racial and ethnic distribution of fra(X) have existed because most early cases were discovered in English-speaking countries of predominantly Anglo-Saxon ancestry. Later reports have described fragile X in a black male,[26] a Spanish-American family[24] and persons of Japanese, Filipino, Australian aborigine[30] and Jewish origin (T.W.G., F.H., unpublished observation).

The range of intellectual deficit among fra(X) boys and men appears to vary from within normal to severely retarded levels, with most cases being appraised as moderately retarded.[28] Until recently, it was suspected that the presence of the fragile X chromosome in a male invariably caused mental retardation. To date, three reports have appeared of fragile X men possessing normal intelligence.[31-33] Judgments of "normalcy" in these cases, however, were based on informal observation and conversation with a patient or on casual inference, not on careful psychometric evaluation by a psychologist. In any event, these findings have compounded the problems of genetic counseling with fragile X families.

Howard-Peebles, Stoddard and Mims[34] examined four fra(X) males by administering the Wechsler Adult Intelligence Scale, the Illinois Test of Psycholinguistic Ability, the Utah Test of Language Development and the Goldman-Fristoe Test of Articulation. These authors noted a generalized language disability concentrated in auditory reception, auditory sequential memory and in areas of visual and grammatic closure. They found that the type of articulation errors made by fra(X) persons did not differ in type from either a normal or another retarded (that is, Down's syndrome) population. Turner and co-workers[28] reported delays in speech development among fra(X) males and described their speech as having a peculiar quality (that is, being narrative and compulsive).

The question exists as to whether or to what extent heterozygous fra(X) females have dimin-

ished intelligence. Turner and associates[28] report the cases of fra(X) carrier sisters who were "obviously slower" than their three other noncarrier sisters. Turner, Brookwell, Daniels and co-workers[35] investigated 128 mildly retarded schoolgirls in Sydney, Australia, and located five (4 percent) who carried the marker X chromosome. Howard-Peebles[36] has suggested that there may be two types of families with regard to fragile X expression in carrier females. One type does not manifest phenotypic expression; the identification of the fragile site becomes more difficult with increasing age with these persons. The second type is associated with some phenotypic effects, such as reduced intelligence, and the fragile X chromosome can be identified regardless of age. McBride[37] and Jacobs and associates[20] have suggested that the Lyonization (inactive X) hypothesis may eventually provide clues to why some females with fra(X) are retarded and some are not. In any event, most studies to date on the fra(X) chromosome have not reported IQ scores, intelligence tests used or other pertinent psychoeducational information. Further testing will be needed to ultimately clarify the relationships of the fragile X to social functioning levels.

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Refer to: Olson KR, Pond SM, Seward J, et al: *Amanita phalloides*-type mushroom poisoning. West J Med 1982 Oct; 137:282-289

Amanita phalloides-Type Mushroom Poisoning

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In the fall of 1981 the San Francisco Bay Area Regional Poison Control Center received more than 100 calls regarding wild mushroom ingestion. Ten cases, including three fatalities, had all the features of Amanita phalloides *poisoning. Encephalopathy, coma and renal insufficiency occurred in all three patients who died, but did not occur in those who survived. Two of the three patients who died arrived at the hospital late in the course of their illness, and severe gastroenteritis with accompanying dehydration probably contributed to their deaths. The poison control center promoted public awareness of the mushroom hazard through newspaper and television stories and by notifying local health departments. It also has devised a simple form to improve the quality of data collection and to assist in later verification of suspected* A phalloides *poisoning.*

As a ROUND-THE-CLOCK toxicology consulting service, the San Francisco Bay Area Regional Poison Control Center (SFBA-PCC) is frequently called on for advice about patient management after wild mushroom ingestion.

In the fall of 1981, a pronounced increase in the number of mushroom-related calls was noted. From October 1 through mid-December, 96 calls were received, a fivefold increase over the same period in 1980. Among these were ten cases of presumed *Amanita phalloides*-type poisoning, of which three were fatal.

This report describes the clinical findings in the ten poisoned patients, who presented initially with acute gastroenteritis and in whom varying degrees of hepatic injury developed. We review the diagnosis and treatment of this type of mushroom poisoning and the identification of *Amanita* species. We also examine possible reasons for the increased number of ingestions in 1981.

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Reports of Cases

CASE 1. A 45-year-old man camping in the Tomales Bay area of Marin County, California, ate two or three wild mushrooms, having eaten wild mushrooms before without problems. No specimens were obtained for identification, but the patient described them as large, having thick stems and being "whitish." After a delay of eight hours, severe nausea followed shortly by abdominal cramping and profuse diarrhea occurred. On arrival in a local emergency room four hours later,

ABBREVIATIONS USED IN TEXT

ALT=alanine amino transferase
AST=aspartate amino transferase

he was alert but was described as appearing dehydrated. His blood pressure was 108/80 mm of mercury and pulse rate was 88 beats a minute. Hematocrit was 53 percent and leukocyte count 14,400 per cu mm. Urinary specific gravity was 1.023 and urine reaction for protein was 2+. Serum electrolyte values were as follows: sodium 135, potassium 4.8, chloride 109 and bicarbonate 16 mEq per liter. Additional laboratory data are given in Table 1.

Intravenous replacement of fluid was started; 36 hours after ingestion, serum aspartate amino transferase (AST, formerly SGOT) and alanine amino transferase (ALT, formerly SGPT) concentrations were greater than 2,500 units per liter. On the fourth day after ingestion, these levels decreased and he appeared to improve. Intravenous administration of thioctic acid, which had just been delivered, was begun. On the fifth day hiccuping developed. Serum AST and ALT concentrations began to rise again, and by the sixth day the patient was in hepatic coma with a blood ammonia concentration of 425 μg per dl. He had a respiratory arrest, was intubated and mechanical ventilation assistance was begun. Generalized motor seizures occurred on the sixth day, for which he was treated with intravenous administration of diazepam (a total of 20 to 30 mg) and phenytoin. Pancuronium bromide was briefly administered intravenously. The patient never regained consciousness, and electroencephalograms on the 7th, 10th and 12th days after ingestion showed progressive diffuse slowing of cerebral activity to a near-isoelectric study. Concurrently, there was progressive loss of brainstem reflexes, and on the 12th day after ingestion, supportive measures were withdrawn and the patient died. Autopsy showed massive hepatic necrosis, renal tubular necrosis and gross cerebral edema.

CASE 2. An 80-year-old man from Marin County who had picked wild mushrooms after each rainfall for years, made a pasta dish containing several mushrooms. He reportedly ate one or two large platefuls. The following day severe nausea, vomiting and pink, watery diarrhea developed. He was admitted to a local hospital 48 hours after the ingestion with severe dehydration and confusion. The hematocrit was 60.2 percent and the leukocyte count was 19,000 per cu mm. Serum electrolyte values were as follows: sodium 154, potassium 4.6, chloride 119 and bicarbonate 11 mEq per liter. Blood urea nitrogen was 52 mg per dl (normal, 8 to 23) and creatinine 4.3 mg per dl (normal, 0.6 to 1.2). Samples of the pasta were obtained and were positive for amatoxins by the Meixner test (see section on identification).

The patient was treated with intravenous administration of fluid and dextrose, and the metabolic acidosis and electrolyte imbalance were corrected. However, he remained confused and became progressively more somnolent. Serum AST, ALT and ammonia concentrations and prothrombin time all increased progressively (see Table 1). On the seventh day after ingestion he was deeply comatose. Septicemia developed and he remained hypotensive despite fluid replacement and vasopressor therapy. He died on the ninth day after ingestion. At autopsy his liver was small with a micronodular pattern but no fatty changes. The myocardium showed fatty infiltration but had no evidence of a recent infarct.

A friend who had eaten two tablespoons of the pasta had nausea, vomiting and diarrhea the day after ingestion. She was admitted briefly but had normal liver function values and recovered fully by the third day after ingestion.

CASE 3. A 39-year-old man found a large wild mushroom in the Santa Cruz, California, area. Although advised by a relative that it "looked dangerous," he cooked and ate the entire mushroom. After 12 hours severe vomiting and diarrhea developed. Two days after the ingestion, he visited a physician who, because of the patient's severe gastroenteritis and apparent dehydration, advised admission to hospital. The patient refused. On the third day after ingestion, the diarrhea worsened and hematemesis occurred; 12 hours later he was brought to the emergency room of a local hospital unconscious. His blood pressure was unobtainable, and his hematocrit was 31.9 percent. He had a cardiopulmonary arrest in the emergency room, was resuscitated, but had another arrest four hours later. He died six days after the ingestion without ever regaining consciousness.

During the hospital course his blood glucose level fell to 22 mg per dl and his creatine phosphokinase level rose to 22,000 units per liter with positive MB bands. (Additional laboratory data are presented in Table 1.) The electrocardio-

TABLE 1.—*Pertinent Laboratory Data in 10 Cases of Amatoxin-Containing Mushroom Poisoning*

Case No.	Age/Sex	Symptoms*	Onset (hrs after ingestion)	Day After Ingestion	Laboratory Data: AST U/liter	ALT U/liter	Total Bilirubin mg/dl	Prothrombin Time (% of normal)	Blood Glucose mg/dl	Creatinine mg/dl	Treatment/Course in Hospital
Fatal Cases											
1	45/♂	N,V,C,WD	8	1	51	57	..	100	261	1.4	Rehydrated; fresh-frozen
				2	2,500	2,500	3.0	..	..	..	plasma; vitamin K; thioctic
				4	1,020	2,500	4.2	13	132	1.5	acid given from day 4/
				6	4,220	7,272	11.8	29	130	1.6	Encephalopathy; respira-
				8	79	1,465	11.7	28	273	2.2	tory arrest; seizures;
				11	35	260	12.3	41	272	3.8	coma; oliguria.
											Died on day 12.
2	80/♂	N,V,WD	12	2	1,200	..	1.7	..	..	4.3	Rehydrated/
				4	2,410	2,500	11.0	37	140	1.8	Encephalopathy; coma;
				5	1,410	2,475	21.7	48	174	..	intractable hypotension;
				6	..	..	..	38	..	..	supraventricular tachy-
				8	87	610	26.0	59	..	1.8	cardia; oliguria.
											Died on day 9.
3	39/♂	N,V,D	12	4	4,860	..	..	13	65	..	Transfusions of fresh-
				5	2,820	3,220	6.7	22	22	5.8	frozen plasma/
											Massive gastrointestinal bleeding; coagulopathy; cardiac arrest on admission.
											Died on day 6.
Survivors											
4	18/♂	N,V,C,WD	8	1	42	21	..	100	..	..	Supportive; vitamin K;
				2	1,550	992	..	42	163	..	dexamethasone given
				3	5,280	5,100	..	35	..	..	intravenously/
				4	1,900	3,900	..	..	..	..	Intermittent bradycardia
				5	710	2,750	3.6	..	129	0.5	and hypotension, required
				8	153	1,360	3.5	..	133	..	temporary pacemaker.
				9	84	810	3.0	80	..	..	No encephalopathy.
5	21/♂	N,V,C,WD	12	2	718	648	1.2	93	104	..	Supportive care/
				4	..	241	..	100	..	1.2	No encephalopathy.
6	24/♂	N,V,C	12	2	880	913	..	85	..	..	Supportive care/
				3	940	880	..	..	..	1.0	No encephalopathy.
				4	195	472	1.5	94	..	..	
7	29/♀	N,V,C,WD headache	12	1	66	..	0.6	..	139	..	Supportive care; activated
				3	617	..	1.2	..	..	0.9	charcoal given once/
				4	210	..	1.1	100	..	..	No encephalopathy.
8	37/♂	N,WD	12	2	982	..	1.8	93	..	..	Supportive care/
				3	..	1,590	..	..	..	..	No encephalopathy.
				4	..	650	..	100	..	1.2	
9	28/♀	N,V,D	8	1	37	..	1.2	..	145	..	Supportive; activated
				2	592	765	..	..	..	1.3	charcoal given very 4 hrs/
				3	1,229	2,360	1.4	78	..	1.0	No encephalopathy.
				4	650	1,560	1.7	..	..	..	
10	21/♀	N,V,D	24	2	1,052	..	0.5	81	..	..	Rehydrated; activated
				3	2,565	3,735	..	49	..	..	charcoal given every 12
				4	..	5,870	0.8	60	124	0.7	hrs/Sleepy but no signs
				7	..	1,550	..	..	..	..	of encephalopathy.

Abbreviations: AST = aspartate amino transferase (normal, 35 U/liter); ALT = alanine amino transferase (normal, 45 U/liter).

*Symptoms: N = nausea; V = vomiting; C = abdominal cramps; WD = watery diarrhea; D = diarrhea

gram showed nonspecific ST changes without evidence of infarction. Autopsy showed acute massive hepatic necrosis, mucosal necrosis in the small and large bowel, cerebral edema and cerebellar tonsillar herniation. The heart showed fatty infiltration of the subendocardial region and some areas of hemorrhage. The patient's relative who was with him at the time he picked the mushroom brought in a similar specimen, identified by a local mycologist as *A phalloides*.

CASE 4. An 18-year-old man ate approximately ten wild mushrooms that he found while camping in the Santa Cruz area. Eight to ten hours later, nausea, vomiting, abdominal cramps and watery diarrhea began abruptly. He brought a similar mushroom with him to the emergency room of a local hospital and it was identified by a mycologist as *A phalloides*. On admission he appeared mildly dehydrated but was alert. His blood pressure was 110/70 mm of mercury and pulse rate 96 beats per minute. Hematocrit was 48.6 percent and leukocyte count 8,400 per cu mm. He was given fluids intravenously as well as dextrose and dexamethasone. The gastrointestinal symptoms abated, but serum AST and ALT concentrations continued to rise, with a peak AST of 5,280 units per liter on the third day after ingestion (Table 1). He remained alert and awake. On the fourth day after ingestion, he had intermittent severe bradycardia, with a heart rate of 28 to 30 per minute and hypotension necessitating placement of a temporary transvenous pacemaker. Liver enzyme values remained elevated for more than ten days, but he had no symptoms or signs of worsening hepatic failure or of encephalopathy. He recovered without further complications.

CASES 5 through 10. A group of seven Laotian refugees gathered and prepared wild mushrooms from a park in the Santa Rosa, California, area. They and other refugees had frequently gathered and eaten similar mushrooms in the past in this area without ill effects. They stated that in their home country foraging for wild mushrooms was common and that they tested for poisonous species by boiling the mushrooms with rice. Mushrooms that turned rice water red were regarded as poisonous and were not eaten; this batch did not color the water and was consumed. One member of the group ate less than a tablespoon of the dish and remained asymptomatic. In the six others, each of whom ate a sizable portion, nausea, vomiting, abdominal cramps and profuse diarrhea began abruptly 8 to 12 hours after ingestion. All were admitted to a local hospital.

In one patient the ALT reached a peak concentration of 5,870 units per liter (see Table 1); although she was mildly lethargic, there was no other clinical evidence of hepatic encephalopathy. All six patients recovered with supportive care. A sample of the mushroom stew was analyzed by a local biologist who identified all but one specimen as species of the genus *Russula,* which do not contain amatoxins. However, one specimen was a "button" (an immature specimen) that had features of an *Amanita* species.

Diagnosis and Treatment of Amatoxin-Containing Mushroom Poisoning

Many species of *Amanita* mushrooms contain amatoxins (α-amanitine and β-amanitine), cyclopeptides that attack the intestines, liver and kidneys. The characteristic course of amatoxin poisoning has three stages: (1) The first phase is delayed in onset, rarely beginning before six hours and sometimes not until 24 hours after ingestion. Severe abdominal cramping, vomiting and profuse watery diarrhea occur and may cause profound dehydration and circulatory collapse. (2) During the next 24 to 36 hours, there is often a remission in symptoms and patients appear to be recovering. During this so-called latent phase, elevations of liver enzymes persist and may even increase. (3) In the third phase, hepatic damage becomes apparent clinically and jaundice, encephalopathy, hypoglycemia, seizures and coma may occur. Death is due to hepatic and renal failure and to secondary effects on the cardiovascular and central nervous systems.[1] Mortality has been reported as anywhere from 10 percent to 90 percent.[1-3] The range reflects the wide variation both in amounts ingested and in individual susceptibility.

Treatment is primarily supportive, with careful attention to restoration of fluid losses, replacement of clotting factors, prevention of hypoglycemia and minimization of hepatic encephalopathy. More experimental or invasive treatments such as hemodialysis or hemoperfusion, repeated doses of activated charcoal given orally and administration of steroids, penicillin, cytochrome *c* and thioctic acid have been proposed, but to date no controlled clinical studies have been done to confirm their effectiveness.[3] Uncontrolled human trials are unreliable, given the great variability in amount of toxin ingested. Animal studies, when

carefully carried out, show no apparent benefit from thioctic acid.[3,4] Previously our impression was that amatoxin poisoning carried with it a mortality of up to 90 percent. Initial results with the use of thioctic acid thus appeared very favorable. Since then we have concluded that the true mortality is probably closer to 30 percent to 40 percent. Our current opinion is that thioctic acid is not of value in the treatment of amatoxin poisoning.

With other "antidotes," treatment was successful only when given to the animals along with the amatoxin or within the subsequent eight hours[5]; this is probably because most amatoxin is excreted within six hours.[3] It is difficult to extrapolate from these results to accidental poisonings because patients often seek treatment much later.

Discussion of Cases

In this series of ten patients the mortality was 30 percent. In all patients who died, encephalopathy and coma developed and evidence of renal insufficiency was present.

The death rate might have been lower had the patients in cases 2 and 3 sought medical attention sooner. The patient in case 3 arrived at the hospital moribund with severe blood loss and coagulopathy; both might have been corrected or prevented had he agreed to earlier admission to the hospital. At autopsy, the patient in case 2 had a small liver with micronodular changes consistent with cirrhosis. His advanced age and probable lack of hepatic and cardiovascular reserve made recovery from the severe gastroenteritis phase less likely.

The patient in case 1 died despite early and vigorous supportive care. No conclusion may be drawn about the effectiveness of thioctic acid in this case because it was not started until about eight hours after mushroom ingestion. It is unlikely that the diazepam, used to control seizures on day 6, significantly affected the electroencephalographic findings or outcome because the dose was small. Although pancuronium may cause prolonged apnea in patients with oliguria and hepatic insufficiency, it would not be likely to cause the electroencephalographic changes seen in this patient.

Other mushroom species may produce toxic symptoms; these have been reviewed previously.[1,6] Hepatotoxicity has been described following ingestion of the "false morel" or *Gyromitra esculenta*. This and similar species contain gyromitrin, which is hydrolyzed to monomethylhydrazine. The onset and character of symptoms are similar to amatoxin poisoning. *Gyromitra* species are very distinctive in appearance, with great brain-like convoluted surfaces. They are principally found in the spring or early summer. Only 20 cases of poisoning due to gyromitrin have been reported in the United States since 1900.[6] It is very unlikely that gyromitrin was responsible for any of the cases reported here; all of these poisonings occurred in the late fall, and in no case did the victim describe finding or ingesting such distinctive mushrooms.

Many other species of mushrooms may cause gastrointestinal upset. However, symptoms occur shortly after consumption and do not result in hepatotoxicity.

Although confirmation by direct examination of specimens or assay for amatoxins was not possible in each case, it is highly likely that amatoxin poisoning was responsible for these illnesses. The onset and character of symptoms, the delayed hepatotoxicity, the description of the mushrooms and the time of year all implicate amatoxin-containing *Amanita* as the cause of poisoning.

Identification of *Amanita* Mushroom Species

Several factors may account for the increase in ingestions of amatoxin-containing mushrooms. First, mycologists are finding *A phalloides* in larger quantities over greater areas of California. Second, there are growing numbers of amateurs interested in foraging for fungi to use for food or for hallucinogenic effects. Some of these collectors may naively sample unidentified species, and others may mistake a toxic for an edible member of the *Amanita* genus (for example, *Amanita calyptroderma*). Third, early and heavy rains followed by warm weather in the fall of 1981 were responsible for an increase in the total number of mushrooms growing in northern California.

The amatoxin-containing amanitas that are commonly found in the western states are *A phalloides* (California, Oregon), *Amanita ocreata* (California) and *Amanita verna* (Washington, questionably California). There are other species of *Amanita* with different toxicologic properties that do not contain amatoxin, for example, *Amanita pantherina* and *Amanita muscaria*; their toxicology is not reviewed here. However, all of these mushrooms have common morphologic characteristics that may be used to classify them

in the *Amanita* genus. The description offered here cannot be used to differentiate among the amanitas or to exclude the possibility of amatoxin ingestion because other non-*Amanita* sp may contain amatoxin (for example, several species of *Galerina, Cortinarius, Conocybe* and *Lepiota*).[6] However, mushrooms that fit the description should be suspect, and the ingestion of any *Amanita* mushroom is ill-advised.

The *Amanita* mushrooms undergo development from a membrane-covered egg stage to a full-sized specimen with stem and open cap (Figure 1). At its early stage, the *Amanita* may easily be mistaken for an edible puffball unless it is cut open to reveal the developing stem, cap and gills inside. As the stem elongates, the membrane breaks and may sometimes be seen on the cap as a patch or warts, depending on the species. This feature is not commonly seen in *A phalloides*. As the mushroom matures, the cap opens outward and tends to flatten with age. As it does so, a second membrane pulls away from the undersurface of the cap to expose the gills. This membrane usually persists as a ring around the midportion of the stem. The gills of *Amanita* sp are white and do not attach to the stem. This can be seen by twisting the stem off the cap to leave the gills intact with no part remaining on the stem itself. An extremely important distinguishing feature of the amanitas is the volva at the bottom of the stem. This is a cuplike membrane around the bulbous base of the mushroom. Unfortunately, it is frequently left behind because the inexperienced collector breaks the specimen off at the stem.

Color is not a very reliable characteristic for identification because it may vary with weather, soil conditions, age and other factors. The cap of *A phalloides* is usually olive yellow or olive brown, whereas that of *A ocreata* is initally white and then turns orange-buff and that of *A verna* remains white.

Although there are many excellent mushroom guidebooks,[7,8] a clinician should confirm the identity of a suspicious mushroom through a local expert. Often a poison control center, a university biology department or a mycological society can assist (in the San Francisco Bay Area, call Dr. Harry Thiers, San Francisco State University, telephone [415] 469-2439).

If possible, it is most helpful to obtain a specimen of the ingested mushroom. An experienced mycologist also may be able to make the identification from spores seen in the vomitus, gastric

Figure 1.—Development of an *Amanita* showing "button" (far left), often mistaken for edible puffball, and mature specimen (far right). (Reproduced with permission from Lincoff and Mitchel.[6])

aspirate or leftovers of the meal itself. Few laboratories are set up to do chromatographic analysis of the mushroom.

A recently evaluated field test for amatoxins described by Meixner consists of rubbing a piece of the mushrooom cap onto newsprint, which is then allowed to dry. A drop of concentrated hydrochloric acid is applied to the paper and yields a bluish-green color if amatoxins are present. The test is highly sensitive, but a negative result should not be used to indicate edibility of a mushroom.[9]

It is apparent from the cases reported here that amateurs should be extremely careful about which mushrooms they choose. So-called rules of thumb, such as the Laotians' rice water test, are unreliable. Unfortunately, untrained persons continue to believe that a poisonous mushroom will tarnish a silver cooking spoon, that a mushroom with nibble marks left by an animal must be safe or that cooking or processing *A phalloides* will destroy its toxins.

The Poison Center Response

All of the reported cases were originally received through the San Francisco Bay Area Regional Poison Control Center. Consultation was obtained quickly with the backup physician staff of the Clinical Pharmacology Unit at San Francisco General Hospital Medical Center. In addition, the public health division of the California Department of Health Services was notified so that investigation and preventive measures could be initiated. This "epidemic" was also reported to local news agencies, resulting in several television and newspaper reports warning the public against consuming wild mushrooms.

A review of mushroom-related calls received in our poison center over the past three years was attempted. However, retrospective verification of suspected amatoxin cases was difficult because

MUSHROOM-RELATED CALL DATA FORM

Poison Control Center Case #_____ Date _____

☐ ASYMPTOMATIC
☐ child ☐ adult ☐ emesis advised ☐ asymptomatic on follow-up

☐ SYMPTOMATIC—hallucinations or neuropsychiatric symptoms
Onset ____ hours after ingestion Follow-up 1 day: ☐ symptomatic
☐ asymptomatic

☐ SYMPTOMATIC—simple gastroenteritis, self-limited
Onset ____ hours after ingestion Follow-up 1 day: ☐ symptomatic
☐ asymptomatic

☐ SYMPTOMATIC—possible amatoxin-type poisoning
Onset ____ hours after ingestion Admitted ____ hours/days after ingestion

ON ADMISSION:
Symptoms: ☐ abdominal cramps ☐ vomiting ☐ other _____
☐ diarrhea (describe severity: _____

Exam: ☐ alert ☐ lethargic ☐ comatose ☐ dehydrated ☐ seizures

Labs: AST ____ prothrombin time ____ ammonia ____ glucose ____
ALT ____ creatinine ____ BUN ____ CPK ____

3-DAY FOLLOW-UP: (____ days after ingestion)

Exam: ☐ alert ☐ lethargic ☐ comatose ☐ seizures ☐ other ____
_____

Labs: AST ____ prothrombin time ____ ammonia ____ glucose ____
ALT ____ creatinine ____ BUN ____ CPK ____

☐ REQUIRES LONGER FOLLOW-UP

MUSHROOM IDENTIFICATION:

Description: _____

☐ original specimen ☐ similar mushroom specimen ☐ confirmed by mycologist

☐ Meixner test used ☐ positive ☐ negative
(Rub mushroom cap on newsprint, allow to dry; add 2-3 drops of concentrated hydrochloric acid—blue-green color may indicate amatoxins)

OUTCOME: ☐ survived ☐ died

COMMENTS/TREATMENT: _____
_____
_____

Figure 2.—Mushroom-related call data form. Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; exam = examination; labs = laboratory data.

data collection was frequently incomplete. A special mushroom call data form was devised (Figure 2). It should improve our ability to collect essential information and to verify suspected amatoxin poisonings.

Conclusion

Identification of mushrooms by nonexperts, particularly by telephone, is unreliable. Even though *Amanita* sp have distinctive characteristics, there are several other genera of mushrooms that contain amatoxins, as noted earlier.

Our poison control center recommends that in all cases of wild mushroom ingestion, regardless of the description, emesis be induced with syrup of ipecac as soon as possible. When mushroom description or clinical presentation (or both) strongly suggests an amatoxin-type poisoning, we recommend thorough gastrointestinal evacuation by emesis, administration of cathartics and repeated doses of activated charcoal. Nasogastric tubes are too small to remove mushroom pieces and should not be used. Along with intensive supportive care, specimens of the ingested mushroom should be sought and identification by an expert obtained. At present, available evidence does not support the use of other treatments such as dialysis, penicillin, steroids or thioctic acid.

Our experience shows how a poison control center can serve (1) as a resource for the immediate care of a poisoned patient, (2) as an agency for data collection and review that promotes recognition of a new health hazard and (3) as an early warning system for state health agencies, the professional community and the public.

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Nuclear Magnetic Resonance Imaging: Current Capabilities

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Nuclear magnetic resonance imaging can produce tomographic images of the body without ionizing radiation. Images of the head, chest, abdomen, pelvis and extremities have been obtained and normal structures and pathology have been identified. Soft tissue contrast with this method is superior to that with x-ray computerized tomography and its spatial resolution is approaching that of x-ray computerized tomography. In addition, nuclear magnetic resonance imaging enables us to image along the sagittal and coronal planes directly, and it does not produce obscuring artifacts by bone.

NOT SINCE THE INTRODUCTION of x-rays into medicine has there been so much excitement as with the realization that imaging by nuclear magnetic resonance is possible. A presentation on nuclear magnetic resonance (NMR) to a medical audience packs an auditorium. Every major x-ray company and other companies in the business of medical imaging have major investments in programs to develop nuclear magnetic resonance equipment. In addition, almost every university in this country has either a program or an agreement with some major company to test their equipment and to do research in nuclear magnetic resonance medical imaging. Although equipment costs range between $800,000 and $1.5 million, multiple orders have already been issued for such purchase.

Physics

The principle of nuclear magnetic resonance is based on the property of nuclei that have an odd number of protons or neutrons, or both, to behave as magnets.[1,2] In the absence of a magnetic field, these nuclei will rotate with their axes pointing in random directions. When they encounter a strong magnetic field the nuclei will tend to align themselves with that field. Hydrogen is generally used for nuclear magnetic resonance imaging as it is the most sensitive to NMR, is ubiquitous and is abundant in the body. If weak radio waves of the proper frequency are applied to nuclei aligned in a strong magnetic field, they will flip and align themselves against the field. In a uniform magnetic field, as the nuclei flip back to their original alignment they will emit a radio signal that has the same frequency as the one whose energy was absorbed. The frequency of the radio wave that causes resonance is specific for each element and is proportional to the strength of the magnetic field. In a field of 3.5 kilogauss, hydrogen will resonate at 15 MHz. Because the frequency of the radio waves emitted is proportional to the magnetic field strength, if the field is made nonuniform in a known manner, then the frequency of the emitted radio waves will be inhomogeneous and the frequency information locates where the signal originated. For example, the frequency of

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ABBREVIATIONS USED IN TEXT

CT = computerized tomography
NMR = nuclear magnetic resonance

radio signals emitted by nuclei in a strong magnetic field will be higher than the frequency of radio signals emitted by nuclei in a weak magnetic field. By varying the magnetic field in all three dimensions it is possible to map the distribution of hydrogen through the substance being imaged. In addition, the strength of the signal is proportional to the amount of hydrogen present in that location.

The characteristics of the NMR radio signal are not only a reflection of the amount of hydrogen present but also depend on T1 and T2, the so-called relaxation times. These depend on local physical and chemical factors such as molecular structure, temperature, viscosity and elemental composition, among others. These will affect the rate at which nuclei will align with the external magnetic field (T1) and the rate at which nuclear energy emission decays (T2) as the nuclei return to their original alignment. T1 and T2 are constants for different tissues. Pure liquids align at a slower rate and emit for a longer time than liquids containing proteins or emulsified fat.

Although T1 and T2 are constant for various tissues, their imaging differences can be enhanced. Varying the interval between successive excitations will selectively enhance tissues according to T1. If the interval between successive excitations is short, tissues with a longer T1 will emit a weaker signal than tissues with a shorter T1. Varying the time interval between nuclear excitation and the recording of the signal will selectively enhance tissues according to T2. Those tissues that have long T2 times will provide larger signals than those tissues that have a short T2.

In addition to the relaxation measurements, it is also possible to measure flow in blood vessels.[3] Because it takes about 30 ms to acquire the signal from hydrogen nuclei in the volume being imaged, if the nuclei move through the volume quickly no signal will be recorded. If the velocity of the hydrogen nuclei is slower, the signal will be correspondingly stronger.

Human NMR Imaging

Human NMR imaging equipment has been in operation for more than two years. A large variety of normal and abnormal images have been published. When looking at these images, we quickly become aware that the gray scales are not consistent among the images produced by different investigators or even within the same group of investigators.[4-6] This results from the fact that there are several NMR imaging techniques and each technique combines the hydrogen density, T1 and T2 components in different proportions and relations.[5,7] In addition, depending on which technique is used, imaging time can vary from 1 to 30 minutes. Further experience will be needed to determine which techniques are more useful under what conditions.

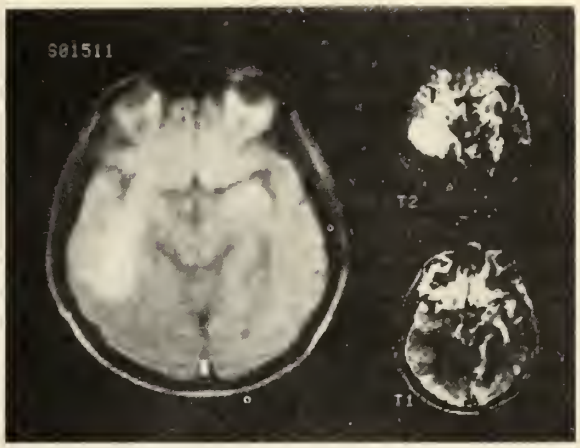

Figure 1.—Transverse NMR pulse echo image through the head of a patient with an ischemic infarct. The gray scale is such that fat appears most intense, other soft tissues intermediate, cerebrospinal fluid darker and air and bone the darkest. On the right are T1 and T2 time images. These are calculated images wherein the brighter the picture element, the longer the relaxation time. The infarct has an abnormally long T2 time.

Extensive imaging of the head has been carried out.[4,6,8-10] NMR images of the brain show spatial resolution approaching that of computerized tomography (CT) and much more soft tissue contrast than with CT. Gray and white matter can be easily separated. The extent of this improved contrast has already been shown in a survey of ten patients with multiple sclerosis.[11] On the average, the use of NMR has provided detection of almost seven times as many lesions as the use of CT has. NMR has also proved useful for imaging the posterior fossa.[4,12] CT images are limited here by artifacts of the skull. These artifacts do not occur with NMR as very little signal is obtained from the skull. In fact, tumors, hematomas and vascular abnormalities have also been imaged in the head (Figures 1, 2).

NMR imaging of the chest has shown several

types of lesions.[6] Masses in the lung can be identified. The extent of tumors infiltrating the mediastinum can be determined because on NMR images a tumor can be easily separated from the great vessels inasmuch as flowing blood usually provides a weaker NMR signal than solid tissues (Figure 3). Esophageal tumors have also been identified.[13]

Cardiac imaging has been surprising. One would suppose that the heart would move too fast to be imaged, but we have been able to obtain satisfactory images of the heart.[5,14] In addition, if part of the myocardium moves slower than its surrounds due to ischemia or infarction, it will produce a stronger signal and a brighter image. Using gating techniques NMR images of the heart have been obtained throughout the cardiac cycle.

Figure 2.—Transverse NMR pulse echo image through the neck of a patient with squamous cell carcinoma of the right side of the neck. The tumor can be seen just adjacent to the right common carotid artery and internal jugular vein, which appear as dark lumens.

Figure 3.—Transverse NMR pulse echo image through the chest of a patient with a tumor just left of the mediastinum. The lumens of the great vessels can be seen.

Abdominal NMR imaging continues to improve at a rapid rate.[4-6,15,16] Spatial resolutions of 2 by 2 mm are currently reported (Figure 4), and even better resolution is expected. Again the tissue contrast is superior to that with the use of CT. Normal anatomic structures are readily recognized. Several groups have imaged the liver and other abdominal organs and have published examples of hepatomas, hepatic metastasis, hepatic infarct, steatosis, cirrhosis, Wilson's disease and dilated bile ducts.[6,17] For some diseases NMR provided a better image, for some CT was better and for some both were equally useful. Other diseases imaged include pancreatitis, pancreatic carcinomas and adrenal tumors.

NMR images of the kidneys visualize the cortex and medulla.[4,5] In a patient with chronic glomerulonephritis, the cortex was noted to be virtually absent in the shrunken kidneys.[5]

Bone is not well seen by NMR because it is relatively hydrogen poor. The marrow cavities usually contain fat, however, which images quite brightly. So whereas bone cannot be seen, it is usually well defined by the surrounding soft tissues and bone marrow. In fact, in patients with giant cell tumors, the NMR images have shown expansion of the marrow cavity, cortical thinning and replacement of the marrow by tumor.[18]

Prospects

In addition to images, NMR provides other information such as T1 and T2 relaxation times. Several groups have shown in vivo in humans and in animals that many pathologic diseases such as

Figure 4.—Transverse NMR pulse echo image through the lower abdomen. The right kidney, muscle planes, aorta and inferior vena cava can be seen, as can the marrow within the vertebral body. Peristalsis blurs the small bowel but does not create artifacts.

tumors, abscesses and hematomas have T1 relaxation times different from normal tissues.[6,17,19,20] In rats it has been shown that the T2 times, along with the T1 times, improve tissue differentiation.[19,20] Further investigations in humans will be required to determine whether the relaxation times can be used for human tissue characterization.

Because NMR can image and differentiate fat from other types of soft tissues and flowing blood, we expect that atherosclerotic plaques and other abnormalities of blood vessels can be imaged and studied. Such plaques have already been imaged in excised vessels.[3]

Although NMR innately provides good soft tissue contrast, several groups are already developing contrast agents, and two are already in use. Mineral oil has been used to increase the NMR signal from the bowel and oxygen has been used to change the signal from the heart.[5,21] Because it is difficult to increase the hydrogen content of most tissues, most contrast agents will be paramagnetic compounds that will instead affect the T1 and T2 times of the hydrogen already present.

It is possible that in the future other NMR-sensitive nuclei such as phosphorus will be imaged in vivo.[22] These other nuclei are less abundant, however, and less sensitive than hydrogen and therefore will not be capable of the resolution of contrast attainable with hydrogen.

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Are Volcanoes Hazardous to Your Health? What Have We Learned From Mount St Helens?

"IS THE VOLCANIC ASH harmful to health?" This was the question posed repeatedly to physicians and public health officials when the violent eruption of Mount St Helens on May 18, 1980, and smaller eruptions later in the summer showered ash over a considerable portion of central, eastern and southwestern Washington state and northwestern Oregon state. The purpose of this review is to report what is known about the health effects of volcanic ash, point out the deficiencies in our knowledge and describe the ways in which the health effects of this unusual form of environmental pollution are being evaluated.

The May 18, 1980, eruption of Mount St Helens was the first major volcanic eruption in the 48 contiguous states of the United States since the eruptions of Lassen Peak in California between 1914 and 1917. As volcanic eruptions go, the eruption of Mount St Helens was quite modest, with only about 2.7 cu km of volcanic rock displaced, compared with eruptions in ancient times that displaced up to 1,000 cu km of material.[1] In the past century, however, only the eruptions of Santa Maria in Guatemala (1902), Krakatoa in Indonesia (1883) and Mount Katmai in Alaska (1912) have surpassed Mount St Helens in magnitude. In terms of energy released, the May 18 eruption was on the order of 100 times the generating capacity of all US electric power stations.[1] Put in another way, the sustained power output of the May 18 eruption may be compared with the serial detonation of 27,000 bombs the size of the one dropped on Hiroshima—nearly one per second for nine hours.

With this amount of energy output, it is not surprising that volcanoes can kill. Probably the earliest report of death from a volcano is to be found in the letters of Pliny the Younger, writing to the historian Tacitus about the death of his father, Pliny the Elder, who succumbed in the eruption of Mount Vesuvius in AD 79.[2] In the 20th century alone, the cumulative mortality from volcanic eruptions is in the region of 55,000, roughly 36,000 of these deaths attributable to the eruption of Mount Pelée in 1902 which caused the destruction of the town of St. Pierre on North Martinique in the French West Indies, and massive flooding and tidal waves.[3] The death toll from the eruption of Mount St Helens was small in comparison, with 62 persons killed or missing. However, this figure would have been considerably higher if the eruption had not occurred on a Sunday when loggers were not on the mountain and if Governor Ray and the US Forest Service had not insisted on keeping the area closed to the public despite vociferous demands for freedom of access.

Causes of Death From the May 18 Eruption

Eisele and co-workers[4] recently reported the autopsy findings in the first 25 bodies recovered after the eruption. The most common cause of death was asphyxia due to inhalation of volcanic

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
EPA = Environmental Protection Agency
OSHA = Occupational Safety and Health Administration
SiO_2 = silicon dioxide
TSP = total suspended particulates

ash; 17 of the deaths were attributed to asphyxia and it was thought to be a contributory factor in two additional deaths. The asphyxia was caused by ash that had mixed with mucus to form occlusive plugs in the upper airways. Two of the victims managed to walk off the mountain and subsequently died in hospital. At autopsy they were found to have a purulent tracheobronchitis that was attributed to inhalation of volcanic gas and particulate matter. Interestingly, a companion who walked off the mountain with these two and was admitted to hospital with them, survived and was eventually discharged. This raises interesting questions about why he should have survived when his companions, who presumably received an approximately equal dose of hot volcanic gases and inhaled volcanic ash, did not.

Thermal burns were directly responsible for some deaths, being a major cause of death in three persons and contributory in two more. In contrast to the persons who died as a result of thermal burns, there was no substantial premortem burning in the victims who died of asphyxia and physical injury. In these victims, there were, however, postmortem thermal changes, with the skin showing a tanning or mummification effect, being leathery and darkly discolored. The portions of bodies that were found buried in ash showed skeletonization and disarticulation, which appeared to be postmortem changes.

This account of the immediate cause of death in the victims of the Mount St Helens eruption is in agreement with the analysis by Thorarinsson[5] of the large number of deaths resulting from the eruption of Mount Vesuvius in AD 79. It seems likely that suffocation from ash is the most immediate hazard and that the accompanying gases, such as sulfur dioxide, though present and noticeable, do not occur in toxic concentrations.

Health Effects of the May 18 Ashfall

Immediately following the May 18 eruption, the process of identifying the composition of the ash began[6,7] and an epidemiologic team from the Centers for Disease Control (CDC) arrived to assist the Washington State Department of Social and Health Services to evaluate the acute and potential long-term health effects.[8] This involved setting up a surveillance network that included 18 main hospitals in the ashfall area of central and eastern Washington, with nine hospitals in the affected area of the state being added after the May 25 eruption. Hospitals were contacted daily by telephone for total numbers of emergency room visits and other admissions for respiratory and other illnesses.

For the week after the May 18 eruption and for the following two weeks there were appreciable increases in emergency room visits and hospital admissions for respiratory complaints in the areas of the heaviest ashfall (Table 1). After the

TABLE 1.—*Emergency Room (ER) Visits and Admissions for Respiratory Diseases for Washington Hospitals, May-June 1980**

Location (No. of Hospitals)	*Ashfall, mm*	*ER Visits/Admissions*				
		May 11-17	*May 18-24*	*May 25-31*	*June 1-7*	*June 8-14*
Eastern Washington						
Ritzville, Moses Lake and Othello (3)	30-70	14/12	72/35	31/12	14/8	14/8
Yakima (2)	8	49/15	150/33	99/19	101/21	102/16
Pullman, Soap Lake, Ellensburg and Ephrata (4)	5-10	14/6	24/7	15/14	18/8	13/10
Spokane (2)	3-4	15/9	55/17	61/14	45/9	36/16
TOTAL		92/42	301/92	206/59	178/46	165/50
Western Washington						
Centralia and Chehalis (2)	8-10	19/6	31/7	62/9	33/5	27/6
Longview (2)	1-2	62/31	54/14	85/25	51/16	53/16
Aberdeen (2)	0.3-0.5	76/10	77/12	95/19	71/20	80/14
McCleary and Shelton (2)	Trace	19/6	11/4	20/6	11/4	10/7
TOTAL		176/53	173/37	262/59	166/45	170/43

*From Baxter et al.[8]

May 25 eruption, there was an increase in the affected areas in emergency room visits, but not in hospital admissions, for respiratory complaints. The main reasons for the increase in emergency room visits seem to have been airways-related problems, such as bronchitis and exacerbations of asthma.[8]

Although respiratory problems were the most common diagnoses, there was also an appreciable increase in the number of visits for eye irritation and abrasion, foreign bodies and conjunctivitis during the first two weeks after the eruption.[8]

These data collected by the CDC and the Washington State Department of Social and Health Services certainly bear out the clinical experience of many of the physicians in practice in the affected areas. However, it would be a mistake to place too much faith in the actual numbers because the disruption of normal life was so great, with travel very hazardous and many physicians' offices closed, that it is hard to know whether the numbers obtained were in fact an underestimate of the real extent of the problem or an overestimate.

An Educated Guess About the Health Hazard

In evaluating the potential risk of an inhaled particulate, the crucial questions that must be answered relate to the size range and composition of the inhaled material, and to the total amount inhaled. The size range is important because this determines the site of deposition in the airways and alveoli. The composition and total amount inhaled are important because they influence the way in which the lungs' defenses cope with the invader.

First is the question of the size range. The first published report of the particle size distribution of the ash was that of Fruchter and co-workers[6] who showed that the particle size distribution of the fallen ash was complex and related to the distance from the volcano. Of particular importance in relation to the effect on the lungs was the finding that between 94 percent and 99 percent of the particles, by count, were within the respirable range (less than 10 μm) in samples taken at different sites across Washington state. There was little doubt, therefore, that most of the ash particles were small enough to penetrate into the alveoli.

Second is the composition of the ash. Because of the critical importance of this question, it was addressed by countless numbers of investigators, working singly in the solitude of their basements or in large laboratories with sophisticated facilities. The major concern related to the free silica content. The fallen ash had a dacitic (high silica) composition. However, most of the silica was in the form of silicates,[6] which are generally not thought to have much fibrogenic potential. The form of silica with the greatest fibrogenic potential is free or crystalline silica (silicon dioxide, SiO_2), which exists in three polymorphs, quartz, tridymite and cristobalite, listed in increasing order of fibrogenicity. The crystalline silica content of the Mount St Helens ash proved to be quite difficult to quantitate because of considerable analytical problems in separating the crystalline silica from the silicates. Initial estimates of the crystalline silica content ranged from less than 3 percent[6] to about 20 percent. This controversy was eventually resolved by a round robin organized by the National Institute for Occupational Safety and Health, Morgantown, West Virginia, in which approximately 25 laboratories analyzed identical samples in a standardized way and using their own methods.[7,8] The consensus that developed from this round robin was that the Mount St Helens ash contained levels of crystalline silica in the range of 3 percent to 7 percent, as part quartz and part cristobalite.[8] No fibrous minerals were found.

Other questions of importance relating to the composition of the ash were the radionuclide and fluoride content. The answers were readily produced and were reassuring: the radionuclide content of the ash was comparable to that of ordinary soil and the leachable fluoride and other heavy metal concentrations were not increased.[6,7]

The third key question in evaluating the potential health effects of the ash related to the inhaled dose. Table 2 shows the average concentrations of respirable dust and the range of dust concentrations measured by the National Institute of Occupational Safety and Health industrial hygienists in a variety of occupational settings in June 1980. To put these in perspective they should be compared with existing criteria for inhaled particulates and silica. The relevant criteria are therefore the ambient air quality standards of the Environmental Protection Agency (EPA) for particulates[9] and the National Institute of Occupational Safety and Health recommendations for occupational environmental exposure limits for crystalline silica.[10]

The EPA standards for particulates are as follows: primary air quality standard, 0.260 mg per

cu m; air pollution alert, 0.375 mg per cu m; warning, 0.625 mg per cu m; emergency level, 0.875 mg per cu m, and significant harm level, 1.0 mg per cu m. It is important to point out that these standards are set for industrial particulate emissions, which are usually associated with other airborne pollutants such as sulfur dioxide and the oxides of nitrogen. It is therefore not clear whether these standards are at all relevant to airborne volcanic ash, especially in a rural setting where the levels of other airborne pollutants are probably negligible.

Rather than using the EPA's ambient air quality standards for particulates, a reasonable argument might be made for using the standards of the American Conference of Governmental Industrial Hygienists for nuisance dust,[11] as the volcanic dust does not constitute an industrial emission. These standards set the permissible respirable dust level at 5 mg per cu m time weighted average, with a total dust level of 10 mg per cu m time weighted average. This means that the permissible dust level over a given period—for example, a work shift—must have an average of less than 5 mg per cu m for respirable dust and less than 10 mg per cu m for total dust. These standards are used in a number of dusty occupations, for example, that of grain workers. However, they are not applicable to volcanic dust inasmuch as one of the important criteria of a nuisance dust is that it is not capable of causing pulmonary fibrosis. Because the crystalline silica content of the ash of 3 percent to 7 percent makes the volcanic dust potentially fibrogenic, it is clearly not in the nuisance dust category.

The occupational and environmental standards for crystalline silica have been set by the Occupational Safety and Health Administration (OSHA) and occupational environmental exposure limits recommended by the National Institute of Occupational Safety and Health.[10] The OSHA permissible exposure level is calculated from the formula

$$\frac{10}{\%\ \text{respirable free } SiO_2 + 2}$$

mg per cu m. For example, assuming the volcanic dust contains 6 percent respirable crystalline silica, the OSHA standards would therefore permit exposure over a working lifetime to dust levels of 1.25 mg per cu m. The National Institute of the Occupational Safety and Health recommendation for an occupational exposure limit for crystalline silica is 50 μg per cu m time weighted average. These levels would be reached by exposure to respirable dust concentrations of just above 0.8 mg per cu m with a 6 percent crystalline

TABLE 2.—*Total and Respirable Dust Levels for Different Occupations, June 1980**

Job	*Total Dust mg/cu m mean (range)*	*Respirable Dust† mg/cu m mean (range)*
Cleanup Crews		
Hand-shoveling and sweeping	2.65(0.64-6.46)	0.46(0.02-2.08)
Sweeper-truck or broom-truck drivers	5.50(0.60-23.1)	0.64(0.03-2.83)
Front-end-loader operators	...(6.17-63.6)	0.50(0.21-0.96)
Grader operators	5.96(0.01-31.9)	0.56(0.01-2.33)
Water-truck drivers	1.48(0.23-6.14)	0.21(0.04-0.64)
Truck drivers	...	0.19(0.10-0.37)
Manual hosing	...	0.05(0.03-0.06)
Rubbish Worker	9.01(0.73-25.5)	0.67(0.11-5.51)
Idaho Forest Worker	...	0.48(0.01-2.46)
Agricultural Worker	1.42(0.79-3.20)	0.44(0.01-1.39)
Law Enforcement Personnel	0.57(0.04-4.17)	0.10(0.01-0.23)
Area Samples		
Homes	0.09(0.03-0.20)	0.03(0.01-0.08)
Schools	0.30(0.20-0.50)	0.06(0.01-0.11)
Commercial establishments	0.30(0.11-0.44)	0.09(0.03-0.20)
Autos	...	0.10
Combines		
With air-conditioned cabs	5.82(4.24-8.20)	0.40(0.17-0.74)
Without air-conditioned cabs	...	2.24(2.20-2.38)
Trucks	2.10(1.70-2.75)	0.35(0.21-0.50)

*Data obtained by National Institute of Occupational Safety and Health industrial hygienists as reported in the Centers for Disease Control's Mount St Helens Volcano Reports Nos. 12 and 17.[7]

†Respirable dust particles collected on a 37 μm polyvinyl chloride filter after passing through a 10 μm cyclone.

silica content. At these levels, according to the epidemiologic data available at the time the standards were set, silicosis would not be expected to develop in an occupational setting over the course of a working lifetime. However, more recent epidemiologic data[12] obtained from the Vermont quarry workers on whom the original standards are based[13-16] cast doubt on the validity of the original longitudinal data, some of which may have been flawed by a leaky spirometer. The environmental and occupational standards for silica exposure therefore probably need to be reexamined in the light of the new data.

How do these standards relate to the environmental conditions in the ashfall areas during the spring and summer of 1980 and to occupational exposure during the cleanup phase following the eruptions (shown in Table 2) and the exposures received by the loggers involved in the salvage operations of the lumber on Mount St Helens? The occupations that had an average respirable dust concentration of 0.45 mg per cu m or more exceeded the National Institute of Occupational Safety and Health recommended exposure limits (assuming a crystalline silica level of 6 percent) of 0.8 mg per cu m 15 percent to 31 percent of the time. If exposures at this level were continued for many years and were not reduced by the use of respiratory protection, these workers would be expected to be at increased risk of silicosis developing.

These occupational data were obtained in 1980. Very few occupational groups have had continued exposure to appreciable dust concentrations since the cleanup was completed in the late summer of 1980. Exceptions to this are the loggers who have continued to work on the salvage operations, retrieving the fallen timber off the mountain, and agricultural workers in eastern Washington.

Compared with some of the occupational exposures, the environmental exposures were modest. Peak levels of total suspended particulates (TSP) were indeed very high in some areas, especially in the path of the plume where TSP levels in excess of 30 mg per cu m were recorded.[7] Because the Environmental Protection Agency's primary air quality TSP standard is 0.26 mg per cu m, with the significant harm level set at 1 mg per cu m for a 24-hour exposure, such high TSP levels would be very likely to provoke acute respiratory tract illness in exposed, susceptible persons or exacerbate preexisting chronic respiratory problems. Fortunately, however, the high levels did not persist, though the TSP levels in the ashfall areas were mostly higher than normal throughout the summer of 1980, as noted by Peter Baxter, MD, and Roy Ing, MD, of the Chronic Diseases Division, Center for Environmental Health, Centers for Disease Control, Atlanta (personal memorandum, May 3, 1981). This led on a number of occasions to air pollution alerts, when the TSP level exceeded 0.375 mg per cu m.

The very low levels of respirable dust measured in homes and other buildings (Table 2) were reassuring and suggest that the general population did not receive and is not receiving a dose of inhaled ash high enough to cause concern. The relatively low levels of dust measured indoors also lent some credibility to the recommendations that persons with heart and lung disease should stay indoors during and after ashfalls.

How the Lungs Handle Particulates

Part of the process of making an educated guess about the potential health hazard of the volcanic ash must involve evaluating the ways in which the lungs handle particulates in general and, more specifically, how the lungs' defenses cope with particulates containing crystalline silica. The deposition of aerosols in the respiratory tract has been the subject of an excellent recent review by Brain and Valberg[17] and a two-part monograph.[18]

Because the respiratory tract is in direct communication with our environment, it is not surprising that it has elaborate defense mechanisms. For the purpose of describing deposition of aerosols, it is usual to divide the respiratory tract into three anatomically distinct compartments; nasopharyngeal, tracheobronchial and pulmonary. The first line of defense an inhaled particle meets is the nasopharynx where turbulent flow through the narrow passages of the nose enhances inertial deposition. Particles that succeed in penetrating the tracheobronchial compartment, which extends to the level of the terminal bronchioles (0.7 mm in diameter), meet an asymmetric system of dichotomously branching tubes, which encourages inertial impaction of particles at bifurcations and settling of particles on the surface of the airways. The pulmonary compartment includes the respiratory bronchioles, alveolar ducts and alveoli, with a huge surface area but small air spaces. Because the bulk movement of air is very slow in this compartment, sedimentation and diffusion can occur.

As noted above, over 94 percent of the volcanic

ash particles by count were in the respirable range, less than 10 μm. The amount and site of deposition in the lungs are most closely linked to median aerodynamic size. For the particles in the 1 to 10 μm size range, inertial impaction and settling are the major mechanisms of deposition and deposition mainly occurs in the nasopharyngeal and tracheobronchial compartments from which the particles are readily removed by the mucociliary escalator. Very small particles, 0.1 μm or smaller, penetrate the pulmonary compartment and tend to be retained very efficiently; they then take considerably longer to be cleared. Particles in the intermediate size range of 0.1 to 1 μm tend to be retained less avidly in the pulmonary compartment than the smaller particles but, if deposited, are also cleared relatively slowly.

It is important to appreciate that there are large differences between persons in the site of deposition and the amount of an aerosol that is deposited. The deposition is influenced by a number of factors such as the size, shape and density of the particles, respiratory anatomy, breathing pattern, dead space volume and tidal volume. Disease, including smoking-related inflammatory changes, will also affect the deposition. The effect of smoking is particularly important, as shown recently by Cohen and colleagues[19] who demonstrated that the long-term clearance of a magnetic dust (iron oxide) was much slower in smokers than in nonsmokers. In their study, after 11 months the smokers retained about five times more iron oxide dust in their lungs than did the nonsmokers. The implication of these data in terms of the volcanic dust is very clear, namely, that any dust particles small enough to penetrate the pulmonary compartment will stay around longer in smokers than in nonsmokers.

If the dust particles were inert, sizable differences between persons in clearance rates would be relatively unimportant. However, because the dust contains crystalline silica, one could predict that deposition in the respiratory tract will provoke a response from the alveolar macrophages, the main scavenger cells of the pulmonary compartment. Macrophages have an important role in influencing the length of time inhaled insoluble particles are retained in the respiratory tract. If particles that are deposited on airway and alveolar surfaces are not phagocytized, they are more likely to pass through or between epithelial cells to the connective tissue and lymph nodes beneath the epithelium where they are retained longer and therefore have a greater opportunity to cause disease. However, the phagocytic role of macrophages can be compromised by a large number of agents, including crystalline silica.[17,18,20,23] The reason for the cytotoxic effect of crystalline silica is not yet clear. What is important is that the dead or dying macrophages release substances that can attract fibroblasts and elicit fibrogenic responses. Thus, even though a macrophage is a very effective first line of defense in protecting the alveolar surface, it has the potential of injuring the lung. This represents an excellent example of biological backfire in that the very mechanism designed to protect the lungs now becomes the mechanism promoting lung injury.

From this brief review of the lung defense mechanisms most clearly relevant to particulates, we can probably speculate that volcanic ash may cause both acute and chronic respiratory tract problems, the acute problems being irritation of the nasopharynx and airways resulting in hypersecretion of mucus, sore throat and cough, and a bronchoconstrictor response in susceptible persons, with the ash acting as a nonspecific, nonallergenic stimulus. In otherwise healthy persons, these acute effects would be expected to pose a relatively minor health problem. In persons with preexisting lung disease, however, one might predict that the additional insult and burden on the already overloaded or impaired lung defenses might constitute a serious risk. Likewise, in persons with reactive airway disease, the precipitation of an acute attack of asthma or the exacerbation of existing bronchoconstriction may have serious consequences.

The main chronic respiratory tract problem of concern in persons exposed over many years to dangerous levels of inhaled volcanic ash is silicosis, or pneumonoultramicroscopicsilicovolcanoconiosis.[24] As discussed above, there is essentially no risk of silicosis developing in the general population simply because exposures have been too low and the exposure time much too short. Even in the occupational groups having the heaviest exposure, such as the loggers salvaging the timber on the mountain, the dust levels are almost certainly considerably lower now than they were in 1980 because the winter rains and snow in 1980 and 1981 compacted the surface of the ash into a crust, which makes it less likely to resuspend when disturbed by wind or humans.

These speculations must be tested scientifically, however. Several groups have now addressed the

question of the potential fibrogenicity of the dust using a variety of studies in animals and in vitro assays. Fruchter and associates[6] were the first to report in vitro biological tests of the ash. These investigators addressed the question of the toxicity of the ash to alveolar macrophages using lavaged macrophages from New Zealand white rabbits, incubated for 22 to 24 hours with volcanic ash, and using polyvinyl-toluene beads as an inert control and α-quartz as a highly toxic (positive) control. The toxicity of each material to alveolar macrophages was then estimated by counting the viable and nonviable macrophages. They found that the ash samples from a number of sites did not differ significantly in cytotoxicity from the inert control but did differ very appreciably and significantly from the quartz control. They predicted from this study that the ash is not highly fibrogenic. Very similar findings using lavaged human macrophages have been reported by Martin and co-workers.[25,26]

A similar conclusion was drawn by Beck and colleagues[27] who used intratracheal instillation of ash in varying concentrations in hamsters with α-quartz used as the fibrogenic control and aluminum oxide and saline used as the inert controls. The lung lavage fluid was then analyzed using a number of different biologic assays that reflect different aspects of lung injury, such as the inflammatory response and the release of cytoplasmic and lysosomal enzymes. They found that the response of the volcanic ash was certainly greater than that of the saline control but was comparable to the response to aluminum oxide, which is generally considered to be relatively inert. The response to α-quartz, on the other hand, was significantly greater than the response to the ash or aluminum oxide for most of the assays. From these data, they concluded that the volcanic ash, though not totally lacking in biologic effects, does not have great potential for causing pulmonary damage unless exposure is prolonged.

Other animal studies using the same technique of intratracheal instillation[28] and studies administering the dust by inhalation (T. R. Martin, MD, personal communication, University of Washington School of Medicine, April 1982) have come to a different conclusion, namely, that the volcanic ash may indeed cause a fibrotic reaction in the lungs. Thus, Green and associates[28] instilled 10 mg of volcanic ash intratracheally in rats, using saline controls, and then killed groups of the exposed or control rats at periods varying from one day to six months. They observed an initial inflammatory response and, later, granuloma formation with most of the granulomas containing foreign body-type giant cells, and some showing central necrosis. Six months after the instillation, the granulomas were larger and contained more collagen than seen earlier.

Martin and co-workers, using the inhalation approach, have come up with very similar findings. They exposed groups of rats to volcanic ash, α-quartz or clean air for six hours a day for ten days, using respirable dust concentrations (volcanic ash and α-quartz particles) averaging about 100 mg per cu m, intended to represent a "worst case" exposure. Immediately after the exposure, alveolar septal thickening and damage to type I pneumonocytes developed in the volcanic ash-exposed animals. Six months later, septal thickening was pronounced and collagen deposition was evident by light and electron microscopy, but no granulomas were seen.

Can these apparently conflicting results be reconciled? My interpretation of them would be that they clearly show that the volcanic ash does not have nearly the cytotoxic or fibrogenic potential of α-quartz but it undoubtedly does have the ability to cause lung injury if deposited in sufficient quantities. In this regard, it is worth pointing out that the exposures in the inhalation studies and the dose instilled intratracheally were very high, much greater than any exposures encountered in an occupational setting and orders of magnitude greater than environmental exposures. The question of whether lower doses delivered over a longer period will also cause lung injury must still be answered by appropriate studies in animals and humans.

Other Health Effects

This review has concentrated so far on the effect of the volcanic ash on the lungs. It would be somewhat myopic to assume that this is the only organ at risk, though the intimate contact of the lungs with the environment makes this organ most likely at risk.

Other possible health effects might be found on the eyes and on mental health. So far, there is relatively little information about the effects on the eyes apart from the initial data from the CDC survey that showed that the number of emergency room visits to two hospitals in Yakima, Washington, for eye irritation and abrasion, foreign bodies and conjunctivitis increased considerably for the

first two weeks following the eruption.[7,8] Whether the eye irritation progresses to a more chronic inflammatory condition with continued exposure is not yet known.

Likewise, there is still relatively little information about the impact of the volcanic activity on mental health. This may turn out to be a very important issue because a report by the US Department of Interior's Geological Surveys warns of possible further dangerous eruptions and heavy ashfalls[7] and has emphasized that other Cascade Range volcanoes may well erupt in the near future. Indeed, the psychosocial problems that stem from living in the shadow of an active volcano may well turn out to be of greater importance than any effect of the ash on the lungs. Extrapolating from data obtained from other natural disasters, especially those that may persist for prolonged periods or have a potential for frequent recurrences, one might predict that feelings of depression, helplessness and loss of control will be common and that varying amounts of stress, bad dreams, sleep problems, guilt, anxiety and avoidance will be seen.

Looking to the Future

The awakening of Mount St Helens in the spring of 1980 has provided scientists of many persuasions the opportunity to study the behavior of volcanoes and the human response to volcanic activity. Despite the existence and activity of volcanoes throughout the world since the beginning of time, there is relatively little solid scientific data relating to the effect of volcanic activity on health. This question assumes considerable importance for those living in the western United States with the realization that a number of the Cascade Range volcanoes are still active and that a sizable population mass is potentially at risk.

We certainly know more about the health effects of volcanic ash than we did in May 1980, but we still do not know nearly enough to be able to give reasoned advice based on solid scientific evidence to public health officials. The advice given at the time of the ashfalls is still appropriate, namely, to minimize exposure to ash by staying indoors when feasible and by using masks approved by the National Institute of Occupational Safety and Health when out in the ash.[7] These have proved to be remarkably effective in reducing the dose of inhaled ash. Deposition of the ash in the lungs can also be minimized by nose breathing. Conversely, the deposition in the lungs will be maximized by exercising vigorously while stirring up the ash and mouth breathing. Jogging and other forms of vigorous outdoor sports should therefore be avoided during and following ashfalls. Outdoor workers who are constantly exposed to the ash should wear adequate respiratory protection and goggles if eye irritation is a problem. Contact lenses should not be worn when dust levels are high.

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Immunoglobulin A and the Kidney

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *The case presentation is by Mr. James Kahn.*

MR. KAHN:† The patient is a 37-year-old man who was admitted because of failing memory and progressive renal failure. He had been admitted to another hospital 17 years earlier for evaluation of hematuria associated with frequent upper respiratory tract infections. Renal biopsy was done then and was nondiagnostic, although he was told he had glomerulonephritis. A number of years later, 3½ before the present admission, his blood urea nitrogen (BUN) was noted to be 31 mg per dl and creatinine was 1.7 mg per dl. Creatinine clearance at that time was 38 ml a minute. Results of analysis of urine were significant for proteinuria (3+) and hematuria (1+). The urine sediment contained five oval fat bodies and 10 to 30 erythrocytes. Six months before admission his BUN was 54 mg and creatinine was 4.5 mg per dl. On admission, the BUN was 98 mg and creatinine was 10.5 mg per dl.

The past medical history and review of systems were noncontributory. There is a family history of hypertension but none of kidney disease.

On physical examination, his blood pressure was 180/120 mm of mercury, pulse rate 80 per minute, respirations normal and he was afebrile. Results of the physical examination were unremarkable except for a harsh grade 2/6 holosystolic murmur that was heard best at the third left intercostal space along the sternal border and did not radiate.

Laboratory studies included a urine analysis that showed 3+ hemoglobin, 1+ protein, 10 to 30 erythrocytes per high power field and one erythrocyte cast. Creatinine clearance was 18 ml a minute. He had a hematocrit of 27 percent. Findings on a roentgenogram of the chest, an electrocardiogram and an echocardiogram were all normal. An x-ray study of his abdomen showed the kidneys to be 10 cm in length. A renal biopsy was done and on light microscopy of the specimen four of seven glomeruli were seen to be completely sclerosed and three out of seven had increased cellularity of the mesangial matrix with capillary sclerosis. Immunofluorescence microscopy showed mesangial staining for immunoglobulin A, C3 and C4. Electron microscopy showed deposits of granular material in the mesangium without any membranous or endomembranous deposits. The diagnosis was IgA nephropathy. Since that time the patient has had an arteriovenous fistula placed and is being treated with hemodialysis.

DR. SMITH: *Dr. James Naughton will discuss the case.*

DR. NAUGHTON:‡ The case presented today is an example of that spectrum of diseases wherein immunoglobulin A is selectively deposited in the renal glomerulus. It is important to realize that

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TABLE 1.—*Clinical Presentations of Renal Diseases Associated With Glomerular IgA Deposition*

Diseases	*Common Syndromes*	*Rare Syndromes*
1. IgA nephropathy (Berger's disease)	Focal glomerulonephritis with macroscopic hematuria (1)*	Nephrotic syndrome (1,2,3)
2. Schönlein-Henoch purpura	Acute glomerulonephritis (2,1)	Malignant hypertension (1,2)
3. Hepatic glomerulonephritis	Chronic glomerulonephritis leading to renal failure (1,2,3)	Rapidly progressive glomerulonephritis (2,1)
	Asymptomatic urinary abnormalities (1,3)	Acute renal failure (1)

*Numbers in parentheses after each syndrome indicate the disease reported to occur with that syndrome in approximate order of frequency.

ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
HLA = human leukocyte antigen
SHP = Schönlein-Henoch purpura
SLE = systemic lupus erythematosus

this case also typifies a relatively common diagnostic dilemma—that is, a patient who is first seen with far advanced renal disease but no established cause for the renal failure. More than 50 percent of all patients with kidney disease in the United States who eventually become candidates for hemodialysis or transplantation have some form of glomerulonephritis as the cause of their end-stage renal disease. In about a third of patients with glomerulonephritis, the disorder has developed as the result of one of the systemic diseases that we recognize as leading to that complication, most commonly systemic lupus erythematosus (SLE), less commonly polyarteritis nodosa, Wegener's granulomatosis, and so forth. In the remaining two thirds of patients with glomerulonephritis who end up with end-stage renal disease in the United States, the cases remain an enigma. We do not know what causes the disease in the vast majority of these patients.

The patient presented here was atypical in that, when initially seen, his kidneys were still relatively normal in size. It is more common in such a patient to find the kidneys already shrunken, which increases the risk of renal biopsy and makes a definite histologic diagnosis more difficult. Therefore, biopsy studies are not done in such a patient and dialysis or transplantation simply is carried out. Because this patient's kidneys were still normal in size and his urine sediment showed abnormal activity, there was a question as to whether he might have a treatable form of glomerulonephritis, and so he had the biopsy procedure. The histologic finding in this case is a relatively common one, as has become apparent in the last decade, though the precise prevalence of this disorder on a worldwide basis varies.

Clinical Features

I want to focus on three disorders that may appear disparate, but that seem to have a common thread of pathogenesis (Table 1). The first is so-called IgA nephropathy, which occurred in the case presented here. The eponym is Berger's disease (the French pronunciation should be retained to avoid confusion with Buerger's disease). The second disorder is Schönlein-Henoch purpura. The third is hepatic glomerulonephritis, a poorly understood condition seen in a variety of patients with end-stage liver disease.

There are four major clinical syndromes that can occur as the result of these three disorders (Table 1). The first is so-called focal glomerulonephritis with recurrent episodes of macroscopic hematuria, not unlike the initial symptoms of this patient. Seventeen years ago he described episodes of macroscopic hematuria associated with upper respiratory tract infection. That is the classic presentation of IgA nephropathy, or Berger's disease.[1]

The second syndrome is chronic glomerulonephritis leading to end-stage renal disease; the case described here also has that clinical course. Initially this was thought to be very uncommon in patients with IgA nephropathy; however, recent studies emphasizing longer periods of follow-up show this outcome more frequently, perhaps in more than 25 percent of cases.[2] The finding of hypertension or significant proteinuria (or both) appears to be predictive of the subsequent loss of renal function.

The third presentation is that of acute glomerulonephritis with the classic features of edema, proteinuria and hypertension. This occurs most commonly with Schönlein-Henoch purpura in children.

The final presentation would be that of asymptomatic microscopic hematuria and mild degrees of proteinuria (generally less than a gram a day).

That characterizes the third group of patients, those with hepatic glomerulonephritis, and also is frequently seen in patients with Berger's disease during the intervals between episodes of macroscopic hematuria. Other syndromes may occur, including nephrosis, malignant hypertension and acute renal failure, but they are uncommon.[3-5]

We will now look at the three diseases in more detail. In 1968 Berger and Hinglais[1] reported on a series of 55 patients, children and adults, who had recurrent episodes of macroscopic hematuria following upper respiratory tract infections. The histologic features that they described in those patients are as follows. On light microscopy there is hypercellularity in the mesangial cells of the glomerulus, whereas the remaining glomerular cells appear normal. The mesangial cell hyperplasia may be apparent in only some glomeruli and not in others, giving rise to the term focal glomerulonephritis. On immunofluorescent staining, the areas of mesangial cell proliferation characteristically stain with anti-IgA, but the glomerular capillaries themselves do not stain for IgA. Variable amounts of IgA, C3 and properdin are also commonly seen. Finally, on electron microscopy one sees electron-dense deposits in the mesangial cells that correspond to the IgA-staining particles on immunofluorescence. The mesangial cell surface comes in contact with blood circulating through the glomerulus in an area where the capillary basement membrane is discontinuous. Apparently these cells possess phagocytic activity and will engulf particles that are otherwise too large to pass through the basement membrane, giving rise to mesangial forms of glomerulonephritis. In the disorders I will review here, the particles that find their way into the mesangial cells contain IgA.

IgA Nephropathy

The clinical features of IgA nephropathy can be summarized as follows: There is a pronounced male predominance with a sex ratio of about 4:1 or 5:1. It is a disease of young adults with the peak ages of onset between 16 and 35. Typically, the episodes of gross hematuria occur after respiratory and gastrointestinal tract infections, and the onset of the episodes of hematuria is within 24 to 48 hours of onset of the clinical symptoms of the upper respiratory tract infection or the gastroenteritis. This would be in contrast to post-streptococcal glomerulonephritis, which has a latent period of 10 to 14 days after streptococcal infection before hematuria appears. Patients with IgA nephropathy have hematuria at the peak of their clinical symptoms.

The prevalence on a worldwide basis is variable. Recent reports from France, Japan and Australia indicate that among patients studied for primary glomerular disease, IgA nephropathy accounts for 20 percent to 25 percent of all cases.[6-8] In a recent series from Australia, IgA nephropathy was found in 12 percent of all renal biopsy specimens, making it the single most common histopathologic finding in renal biopsies in Austrialia.[6] IgA nephropathy appears to be less frequent in the United States, being found in about 5 percent of all biopsy specimens[9] and occurring in perhaps 10 percent to 15 percent of primary glomerular diseases. On laboratory examination, the most common findings are increased levels of serum IgA, which are present in more than half of the patients,[3,8] particularly when the IgA levels are measured at the time of a clinical flare of the disease. Some normal laboratory findings are important: serum complement levels are typically in the normal range, and tests for circulating immune complexes usually give normal findings. There has been a familial trend in some reports wherein several family members have had IgA nephropathy, raising the possibility of a genetic determinant. There are scattered reports from different parts of the world of human leukocyte antigen (HLA) associations, HLA-B35 in one series[10] and HLA-A12 in another,[11] whereas others have reported a lack of HLA association.[3,12] These variable associations probably reflect linkage disequilibrium of A or B loci in certain ethnic groups. For example, in a series of patients from Japan one might find a certain HLA association, but when another investigator examines a European population, that linkage is not present and no association is found.

HLA typing of the D locus has not been carried out in a large series of patients with IgA nephropathy. A recently published letter from France[13] reported that more than half of the patients who present with IgA nephropathy have loci typed at HLA-Dw4. This is the same locus that appears with increased frequency in rheumatoid arthritis and in a variety of other diseases. Although this is only a preliminary communication and it has not been confirmed elsewhere, it is interesting to relate the possibility of HLA-Dw4 association to some of the clinical findings reported in patients with IgA nephropathy. For instance, a Japanese study reports that in 6 of 39 patients with IgA

nephropathy followed for three years scleritis developed.[14] Scleritis, of course, is a well-described complication seen in patients with rheumatoid arthritis. Other clinical associations reported with IgA nephropathy include cyclic neutropenia, mycosis fungoides,[15] dermatitis herpetiformis[16] and asymptomatic pulmonary hemosiderosis[17]; these are primarily isolated case reports.

Schönlein-Henoch Purpura

Description of the second group of disorders, Schönlein-Henoch purpura (SHP), is historically much older. Berger's disease was first described in 1968.[1] If we look carefully at the history of SHP, we will find that it was probably first described in 1808.[18] As is often the case with eponymic diseases, history shows that the person for whom the disease was named has a tenuous claim to that honor. The first two people to describe this disorder—that is, to describe an association of abdominal pain and purpura—were Heberden and Willen in independent reports in 1808. In 1837 Schönlein added arthritis as a third component to the triad of purpuric rash and abdominal pain. It was not until the 1870's that Henoch enters the picture, when he added the presence of gastrointestinal hemorrhage and later that of hematuria to complete the syndrome.

The common clinical findings include a nonthrombocytopenic vasculitic purpuric rash, characteristically found over the lower extremities and the buttocks. There is an old clinical pearl in pediatrics that when a child has acute abdominal pain, one must always look at the skin on the legs and the buttocks for the rash of SHP; children have undergone exploratory laparotomy that may have been avoided by noting the presence of this rash. Arthralgias, abdominal pain, gastrointestinal bleeding and hematuria are the other common features seen in both children and adults, though the disorder is much more common in children. Skin involvement, which is the sine qua non of the disorder, is present in 100 percent of cases, with purpura being vastly the most common lesion seen, though a maculopapular rash also occurs. Children may have local cutaneous edema, particularly very young children. This observation is credited to Osler, who emphasized some of the allergic features of the disease, leading to the term "anaphylactoid purpura" as another name for SHP.

Joint symptoms and hematuria are common in adults. The gastrointestinal features, both pain and bleeding, are less common in adults than in children. SHP has a generally good prognosis. Many patients will have a relapsing course; that is, the disease will flare repeatedly, usually after upper respiratory tract infections, and then over a period of years it fades away. Some patients are left with renal impairment. It would appear that roughly 20 percent of adults who have an episode of SHP will be left with mild hypertension or persistent urinary abnormalities, or both, and then in a smaller percentage of those patients, end-stage renal disease will develop. In the pediatric population, about 15 percent of all children who ultimately require dialysis or transplantation have SHP as the cause of their renal failure.[19] That is a far higher percentage than would be seen in the adult population. The histology of this lesion is essentially identical to that of Berger's disease, predominantly mesangial cell hyperplasia with mesangial deposition of IgA-containing immune complexes.

Hepatic Glomerulonephritis

It has been observed over the last decade that patients with a variety of end-stage liver diseases commonly show asymptomatic urinary abnormalities on careful analysis of the urine, chiefly hematuria and proteinuria. Histologic examination of the kidney in these patients, usually done at autopsy, shows the same pathologic features seen in IgA nephropathy and SHP: mesangial deposition of IgA.[5,20] The prevalence of this finding in patients with advanced liver disease is unknown. In the few series that have reported studies of immunofluorescent staining of renal tissue in all patients dying with end-stage liver disease, this histologic picture was seen in more than half the patients studied.[20] These reports are primarily from Europe, as this has not been an area of much interest in the United States. Generally these patients are asymptomatic, renal failure rarely develops as a consequence of this mechanism and, unlike in both SHP and IgA nephropathy, you do not see an association with upper respiratory or gastrointestinal tract infections and flares of the renal disease.

Pathogenesis

The pathogenesis of these disorders is not well understood, but there are four general areas that I will address (Table 2):

TABLE 2.—*Pathogenesis of Renal IgA Disorders*

Immune Complexes (IC)
Circulating IC not detected by Raji cell, Clq binding or conglutinin assays
IC may be detected by anti-IgA assay
Complement
Serum levels usually normal
Variable amounts of C3, properdin and, less commonly, C4 are seen in renal mesangium
Animal model does not need complement to produce the renal lesion
Source of the IgA
No secretory piece or J piece can be routinely shown in renal IgA
Studies on IgA1 vs IgA2 in renal tissue have been conflicting, but probably predominantly IgA1 is deposited
Most evidence currently favors IgA derived from marrow rather than from mucosal sources

- What is the role of circulating immune complexes?
- What is the role of complement?
- Where does the IgA come from?
- Are there pathogenic interrelationships among these three disorders?

Immune Complexes

IgA-containing complexes are seen in the mesangial cells in all three disorders. The standard tests for circulating immune complexes, including the Raji cell, the Clq binding assay and the conglutinin assay, are usually negative in patients with IgA nephropathy and SHP.[21] Recent reports suggest that immune complexes can be detected in these patients by using an anti-IgA assay.[22] Whether they are detecting true immune complexes (that is, combinations of IgA and an antigen) or whether they are detecting aggregates of IgA (polymeric IgA) remains to be determined. Serum IgA levels are elevated in most of these patients and polymeric (aggregates of the smaller 7S molecules) IgA levels are also elevated. It is also possible that the immune complexes are formed in the mesangial cells by the separate trapping of circulating antigen and antibody.

Complement

Serum complement levels are classically normal in these disorders.[3] This can be helpful in excluding poststreptococcal glomerulonephritis in a patient who has hematuria after an upper respiratory tract infection because patients with poststreptococcal glomerulonephritis are hypocomplementemic. However, immunofluorescence staining commonly shows the presence of C3 and properdin in mesangial cells, but usually not the early reacting complement components, C4 and Clq. This suggests that activation of the alternate pathway of complement may be important in the pathogenesis.

There is now an animal model for IgA nephropathy.[24] It uses an IgA-producing myeloma cell line in mice. The IgA is incubated with dinitrophenol-treated bovine serum albumin, producing an IgA complex that will in turn induce hematuria and the histologic features of IgA nephropathy in mice. There are two important observations from studies in mice: First, the lesion can be induced only by using polymeric IgA. If individual 7S IgA is used, no lesion is produced. Second, if the mice are first depleted of complement by using snake venom and the IgA complexes then administered, the same histologic lesion will develop. This would suggest that complement is not necessary for the pathogenesis of the lesion. This is also consistent with the absence of inflammatory changes that should be seen when there is complement activation; that is, in neither human patients nor in mice is there migration of polymorphonuclear leukocytes into the glomerulus or endocapillary proliferation.

Where Does the IgA Come From?

It is intriguing to speculate that because SHP and IgA nephropathy appear after respiratory and gastrointestinal tract infections, perhaps IgA responses at mucosal barriers are important in pathogenesis. We recognize two kinds of IgA in humans, that which circulates in blood and that found in mucosal secretions. In blood, IgA is present in about one fifth the concentration of IgG, whereas in mucosal secretions IgA represents more than half of all immunoglobulin present in those secretions.

Secretory IgA is derived from a population of plasma cells that exist in the submucosa along the respiratory, gastrointestinal and genitourinary tracts. These plasma cells elaborate a dimer of IgA molecules that are hooked together by a so-called J chain, which also is derived from plasma cells. That is the form in which the immunoglobulin is secreted from the plasma cell into the submucosal space. A product is then elaborated by the mucosal cell itself, a nonimmunoglobulin glycoprotein called secretory component. A secretory

component attaches to the dimer of IgA and enables it to be transported out into the lumen of the mucosal tissue. Therefore, there are several characteristics that would enable one to distinguish secretory IgA from the IgA that is derived from bone marrow plasma cells.

A final observation is that independent of the presence of the J chain, the dimer and the secretory piece, there is another distinguishing feature among all IgA molecules. IgA is classified further as IgA1 and IgA2 based on whether or not the molecule is cleaved by IgA protease. Certain bacteria—for example, pathogenic strains of *Neisseria*—elaborate a proteolytic enzyme that inactivates IgA by breaking the molecule in one area of the heavy chain. IgA1 is inactivated by IgA protease, IgA2 is resistant to IgA protease. Secretions of the respiratory and gastrointestinal tracts contain 50 percent to 60 percent IgA2. This is thought to have evolved because of the selective advantage of elaborating a molecule that is resistant to the IgA protease. The IgA that circulates in blood, however, is only about 10 percent IgA2; the remainder is the protease-sensitive form.

To summarize the data at this point in patients with IgA renal diseases, we have the following observations. If you examine the IgA deposited in the glomerulus there is no secretory piece demonstrable[25]; similarly, J piece is usually not found. These two observations would argue that there is no evidence that the IgA present in the kidney is derived from mucosal secretions. There is conflicting evidence as to whether the IgA in kidney is IgA1 or IgA2. A disproportionate amount of IgA2 in the kidney would argue for a secretory origin. Unfortunately there are two recent papers on this issue that are completely conflicting.[26,27] André and co-workers[26] reported on groups of patients with IgA nephropathy, SHP and hepatic glomerulonephritis and a few patients with SLE who had glomerular deposition of IgA. By their methods they found more IgA2 in the patients with IgA nephropathy, SHP and liver disease, whereas the SLE patients had predominantly IgA1. They concluded that the IgA in the first three disorders was of mucosal origin. At the same time, Conley and colleagues[27] published exactly the opposite results. Using different reagents they found primarily IgA1 in patients with IgA nephropathy and SHP. There has subsequently been a letter published that supports the results of Conley and associates and not André and coworkers' results. In summary, at this time there is no conclusive evidence of a mucosal source for the IgA, despite the relation between respiratory and gastrointestinal tract infections and flares of the renal disease.

TABLE 3.—*Relation of All IgA Nephropathies*

All three disorders are immunohistologically identical
Extrarenal IgA deposition (especially skin) is seen in Berger's disease and Schönlein-Henoch purpura
Serum IgA levels are usually elevated in all three disorders
Polymeric IgA is necessary to create lesions in animal model; a normal liver clears polymeric IgA from the circulation

TABLE 4.—*Approach to Diagnosis*

Analysis of urine to include examination of erythrocyte morphology by phase contrast microscopy
Measure serum IgA level
Take a biopsy of normal skin to determine deposition of capillary IgA
Renal biopsy if renal function impaired or if protein reaction in urine is greater than 1.0 grams/24 hr.

Pathogenic Relationships

Are there pathogenic relationships among these disorders? All three of the diseases have the same morphology (Table 3). That is, IgA nephropathy, SHP and hepatic glomerulonephritis are largely indistinguishable on studies of renal biopsy specimens. In IgA nephropathy and certainly in SHP it is now clear that extrarenal deposits of IgA are very common and are typically seen in skin biopsy specimens.[28] We do not have comparable information on the patients with hepatic glomerulonephritis. Again, there is no apparent association between mucosal infections and renal disease in hepatic glomerulonephritis. The liver disease is therefore somewhat different from the other two disorders. The common pathogenic link to liver disease may be as follows: It appears that normal liver has a specific transport process for picking up polymeric IgA and transporting it from plasma into the biliary tract. It is not clear how much of the IgA in gastrointestinal secretions is derived from that mechanism, but it appears to be significant and is easily seen in experimental animals. If experimental liver disease is induced in a rat by mechanisms as diverse as carbon tetrachloride poisoning or by ligating the common bile duct, there is an immediate increase in circulating IgA, chiefly of the polymeric fraction.[29] Patients with hepatic glomerulonephritis also have elevated circulating IgA levels, again of the polymeric frac-

tion. In advanced liver disease, therefore, the decreased clearance of polymeric IgA may predispose to renal deposition. As stated before, in the mouse model of IgA nephropathy only polymeric IgA would induce renal disease.

Diagnosis

Turning now from the subject of pathogenesis, I will review the diagnostic approach to these disorders (Table 4), emphasizing the use of urine analysis, skin biopsy and renal biopsy. I have already mentioned that serum IgA levels are often elevated in these disorders and, therefore, measuring IgA levels can be an important diagnostic tool. With urine analysis, we are classically taught that when a patient has hematuria, one would suspect a glomerular origin only when either erythrocyte casts are seen, or significant proteinuria is present, or both. In the absence of those two findings, we are taught to pursue a structural evaluation of the urinary tract—cystoscopy, intravenous pyelography and perhaps even arteriography. Recent reports from Australia suggest that simply by examining the morphology of erythrocytes in fresh urine under phase contrast microscopy one can readily distinguish between glomerular and nonglomerular hematuria.[30] Erythrocytes of glomerular origin appear prominently dysmorphic with variations in size, fragmentation and a peculiar form that has the appearance of budding yeast. Erythrocytes of nonglomerular origin are much more regular, occurring as either normal biconcave cells or ghost forms. Fairley and Birch[30] reported on 88 patients who were referred to the Royal Melbourne Hospital for evaluation of hematuria. The ultimate diagnosis was confirmed by renal biopsy and by full urinary tract evaluation in all cases. Of the 88 patients, 58 proved to have glomerular disease by biopsy, and 30 had nonglomerular disease with the usual array of stones, tumors and so forth. This simple technique of analysis of the urine identified virtually all of the patients in both groups. Of the 58 patients with glomerular disease, 55 had completely dysmorphic erythrocytes, whereas 3 of the 58 cases had a mixture of about 80 percent dysmorphic and 20 percent normal erythrocytes. Interestingly, all three of those cases turned out to have IgA nephropathy. None of the 30 cases of nonglomerular hematuria had dysmorphic erythrocytes, however. Although this observation has not been confirmed in the United States, it would appear that a simple modification of the technique of routine urine analysis would enable us to identify patients with glomerular hematuria and completely redirect our work-up at that point as to whether structural lesions or primary renal disease need be pursued. We have begun to use this technique on the renal service at the University of California, San Francisco, and are encouraged by our initial results.

We will next consider the skin biopsy. As mentioned earlier, there are several series now that have shown that patients with SHP and IgA nephropathy commonly have extrarenal deposits of IgA. This has been most carefully examined in a large series reported from Belgium[28] wherein 262 patients with a variety of renal diseases all had skin biopsies. Biopsy specimens were taken of clinically normal skin from the volar aspect of the forearm (biopsies were not done of rashes). Of the 262 patients, 45 had IgA deposition in the skin, and when these results were correlated with the clinical findings, 12 of the patients were found to have SHP, of the remaining 33 patients all but one had IgA nephropathy. The one false-positive result occurred in a case of acute tubular necrosis. There were only three patients in that series in whom results of skin biopsies were negative for IgA, but who had IgA deposition in the kidney and clinical features of IgA nephropathy. This observation is confirmed now by other studies,[3] so that it currently appears that about 90 percent of patients with Berger's disease will have positive findings on skin biopsy.

Anecdotally, our own experience has been somewhat more ambiguous. We have done a few skin biopsies on patients who had histologically confirmed IgA nephropathy but in whom IgA deposition was not found. It is not clear whether results of skin biopsies are more likely to be positive when the disease is active. I think at this point, when confronted with a patient with the appropriate history, recurrent episodes of macroscopic hematuria and dysmorphic erythrocytes on analysis of urine, one should both measure serum IgA levels and do a skin biopsy. If IgA is seen in the skin capillaries and serum levels are elevated, a presumptive diagnosis of IgA nephropathy is then established and one need not pursue it beyond that point.

What about a patient in whom the results of a skin biopsy are negative? How far do you go in this evaluation? I would suggest that if a patient's renal function deteriorates, as determined by a creatinine clearance exceeding 1,000 mg in a 24-hour collection, or significant proteinuria de-

velops, or both, that patient might well be considered for renal biopsy to establish the cause of the disease and to find out whether it is treatable. In the absence of those findings, I think it is safe to simply observe these patients.

Treatment

We can say there is no treatment at this time, which is true. However, a few comments are worth making. There is some evidence in the literature that patients with acute episodes of SHP will have lessening of their abdominal pain and joint symptoms with brief courses of corticosteroids.[18] Corticosteroids and immunosuppressive drug therapy, however, have not been shown to influence the course of renal disease in either SHP[19] or Berger's disease.[3] The most imaginative therapeutic trials to date have come from both Australia and Europe, where a series of patients have been treated with diphenyihydantoin.[3] It was observed more than a decade ago that in many patients treated with this anticonvulsant for the usual clinical indications, levels of circulating IgA fell.[31] In fact, clinically evident IgA deficiency has even been described as a complication of diphenylhydantoin treatment. This led Clarkson and associates[3] to begin administering this drug prospectively in a randomized, controlled study to groups of patients with IgA nephropathy. Unfortunately, the results to this point do not suggest any significant effect on the course of renal function. They have reported that clinical episodes of macroscopic hematuria are decreased in the patients treated with diphenylhydantoin, but otherwise the progression of their renal disease seems to be unaffected. Most patients so treated do have return of their IgA levels to normal. In patients in whom end-stage renal disease develops from IgA nephropathy, histologic recurrence of the disease has been reported following renal transplantation.[7] However, graft failure on the basis of recurrent disease rarely occurs (the first such case has recently been seen on the University of California, San Francisco, transplant service) and the presence of IgA nephropathy should not be considered a contraindication to transplantation.

Summary

We have looked at three diseases that are morphologically similar yet may have diverse clinical features. Within this spectrum of disease, the one that is the most common and most likely to be encountered by internists is IgA nephropathy. There are now several relatively noninvasive techniques that can lead to the diagnosis. Effective treatment is not yet available and, although the clinical course in many of these patients will be benign, progressive renal failure will develop in others.

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Important Advances in Clinical Medicine

Epitomes of Progress—Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Initiation of Anticonvulsant Therapy

THE CHOICE of anticonvulsant medication with which to initiate therapy for epilepsy depends on accurate classification of a patient's seizures. Patients who have primary generalized convulsive seizures are best treated with phenytoin, phenobarbital, primidone or carbamazepine. Patients who have generalized nonconvulsive seizures may be treated with ethosuximide, valproic acid or clonazepam. Partial seizure disorders, including those with complex symptoms, may be treated with phenobarbital, carbamazepine or phenytoin.

The routine use of multiple anticonvulsant medications in the initial treatment of epilepsy is widespread. However, there is no convincing evidence that therapy using several agents is consistently, or even usually, more effective than with a single agent. Therapy with a single agent at optimal doses in previously untreated patients completely controls seizures in 75 percent of patients and the addition of a second medication often does not improve seizure control. Routine administration of multiple anticonvulsant medications increases the likelihood of undesirable drug interactions, or may lead to acute or chronic toxic drug reactions. The situation may also be complicated by the fact that toxic or high therapeutic doses of phenytoin may actually increase the frequency of seizures or precipitate status epilepticus. It is safer and more effective to initiate therapy with a single antiepileptic medication, and to add drugs as needed. If the initial anticonvulsant medication is totally ineffective in controlling seizures, however, that drug should be discontinued and an alternate medication given.

Initial dosage is determined by the choice of anticonvulsant medication. Phenytoin and phenobarbital administration may be begun at the usual maintenance dosage, whereas carbamazepine, primidone, clonazepam, ethosuximide and valproic acid must be given at a low initial dosage and gradually increased to the maintenance dosage. This gradual increase in dosage minimizes transient initial side effects such as gastrointestinal upset, mild ataxia or sedation, and may improve drug compliance.

Carbamazepine and phenobarbital stimulate their own enzymatic degradation, so that initially therapeutic blood concentrations may become subtherapeutic after continued use. For example,

carbamazepine administration is begun at 200 mg a day and increased every two days to a "plateau" dosage of 200 mg four times a day. This dosage may cause a striking initial reduction in seizure frequency. After a time, however, the seizure frequency may increase and be associated with a fall in blood levels so that the dose of carbamazepine must be increased to 1,200 to 1,600 mg a day. A similar phenomenon may occur when phenobarbital is used.

When anticonvulsant therapy is initiated with the administration of phenytoin or phenobarbital at a maintenance dosage, two weeks or more may elapse before therapeutic blood concentrations are achieved. Under some circumstances, it is desirable to attain therapeutic blood concentrations more quickly. In adults, orally administered loading doses of phenytoin (13 mg per kg of body weight) or phenobarbital (10 mg per kg) may be used. Dosage should be adjusted so that therapeutic blood concentrations are maintained. It is important to remember, however, that whereas attaining therapeutic blood levels is an important adjunct to management of patients with seizures, the goal of any anticonvulsant regimen is to control clinical seizures.

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Benign Paroxysmal Positional Vertigo

BENIGN PAROXYSMAL POSITIONAL VERTIGO is the most common type of vertigo seen in our neurotology clinic. Brief episodes of vertigo develop (less than 30 seconds) with position change, typically when a patient turns over in bed, or when bending over and straightening up or extending the neck to look up. Benign paroxysmal positional vertigo can result from head injury, viral labyrinthitis and vascular occlusion, or it may occur as an isolated symptom of unknown cause. The latter is particularly common in elderly persons. This syndrome is important to recognize because in most patients the symptoms spontaneously remit without sequelae.

The diagnosis of benign paroxysmal positional vertigo rests on finding characteristic paroxysmal positional nystagmus after a rapid change from a sitting to a head-hanging position (Dix-Hallpike maneuver). The positional nystagmus occurs usually after a 3- to 10-second latency and it rarely lasts longer than 15 seconds. A burst of nystagmus in the reverse direction usually occurs when a patient moves back to a sitting position. Another key feature is that a patient experiences severe vertigo with the initial positioning but, with repeated positioning, the vertigo and nystagmus gradually disappear (so-called fatigability).

Studies of the temporal bones of a few patients with typical benign paroxysmal positional nystagmus have found basophilic deposits on the cupulae of the posterior semicircular canals. These deposits were typically present on only one side, the side that was undermost when paroxysmal positional nystagmus and vertigo were induced. These cupular basophilic deposits are apparently otoconia released from a degenerating utricular macule. The otoconia settle on the cupula of the posterior canal (situated directly under the utricular macule) causing it to become heavier than the surrounding endolymph. When a patient moves from a sitting to a head-hanging position (a provocative test for paroxysmal positional vertigo) the posterior canal moves from an inferior to a superior position, a displacement of the cupula towards the utricle occurs and a burst of nystagmus is produced. The latency before the nystagmus occurs could be due to the time required for the otoconial mass to be displaced and fatigability may be caused by the dispersing of particles in the endolymph. Consistent with this theory, the burst of rotatory paroxysmal positional nystagmus is always in the plane of the posterior canal of the "down" ear with the fast component directed upward (toward the forehead). Additional support for this concept has come from reports showing disappearance of fatigable paroxysmal positional nystagmus after the ampullary nerve has been dissected from the posterior canal on the diseased side.

The treatment of benign paroxysmal positional vertigo is a difficult problem because the episodes of vertigo are very severe but usually last only a few seconds. To completely suppress these brief bouts with antivertiginous medication, patients would have to be heavily sedated throughout the day, usually an unacceptable circumstance. More than 90 percent of patients with benign paroxysmal positional vertigo have a spontaneous remission within six months, but the episodic vertigo

does recur in a small percentage of patients. As the syndrome subsides patients may complain of positional dizziness or lightheadedness for a time, without easily recognizable nystagmus with change of position.

Once the diagnosis is clear, a simple explanation of the nature of the disorder and its good prognosis gives a patient a great deal of relief. Preliminary studies indicate that having a patient make repeated positional changes from a sitting to a lateral position several times a day causes the episodic vertigo to remit faster than when a patient avoids positional changes. In rare cases of intractable positional vertigo, transection of the posterior ampullary nerve has resulted in prompt and complete remission of symptoms. Severe sensorineural hearing loss is a possible complication of such a procedure, however.

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Lorazepam: A New Antiepileptic Drug in Status Epilepticus Therapy

STATUS EPILEPTICUS is a serious and often an acute, life-threatening neurologic disorder. Although currently available drugs for treatment of status epilepticus are often effective, they also have some undesirable properties. Phenobarbital often impairs consciousness and depresses respiration. Phenytoin has to be given by slow intravenous injection and it also is relatively slow acting. It may produce hypotension, cardiac arrhythmia and conduction block. The anticonvulsant effect of a single intravenous injection of diazepam is of short duration because it is rapidly distributed through tissue.

Lorazepam has been used as a premedicant or induction agent in anesthesia and to treat acute symptoms of severe anxiety. Recent clinical studies have indicated that lorazepam appears to be an ideal drug for treatment of status epilepticus. Intravenously given lorazepam is rapidly effective and has a prolonged duration of action with minimal side effects. The overall success rates are 80 percent to 100 percent. In most patients repeated injections are not required. Lorazepam is effective in treating both generalized and partial status epilepticus, but it is less effective in managing status epilepticus due to myoclonic epilepsy, Lennox-Gastaut syndrome or seizures associated with acute destructive cerebral pathologies. The onset of action following intravenous administration is usually within one to three minutes, and the duration is at least 2 hours but often longer than 48 hours when previous anticonvulsant medication is continued. Electroencephalography shows that lorazepam is capable of preventing the spread of seizures and of suppressing the epileptic discharges of the focus. Complications of the therapy are minimal and temporary: sedation, agitated confusion, tremor, hallucination, ataxia and vomiting. In a study by Walker and co-workers on 25 patients, however, there was one case of transient respiratory arrest.

Lorazepam is a benzodiazepine derivative. It is given by slow intravenous injection for two minutes, the doses ranging from 2.5 to 8 mg, but usually 4 mg is given. Administration of the drug can be repeated in 15 minutes if status epilepticus is not controlled. The drug is highly protein-bound, has a half-life of 8 to 26 hours and it is rapidly conjugated and excreted by the kidney. It is less lipid soluble than diazepam and, consequently, its tissue distribution is less rapid and extensive. This allows longer duration of action.

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Aspirin Use in Stroke Therapy

TRANSIENT ISCHEMIC ATTACKS of the brain due to platelet emboli, typically forming on atherosclerotic lesions of extracranial arteries, have played a major role in stroke therapy. In up to half of thrombotic strokes these warning symptoms yield to both medical and surgical treatments that can avert devastating strokes. Medical therapy includes administration of antiplatelet aggregation drugs and anticoagulation. Antiplatelet aggregation agents are favored because they are less often attended by complications such as hemor-

rhages. "Platelet stickiness" can be reduced by a variety of drugs such as aspirin and dipyridamole.

Although a Canadian study showed a reduction of strokes after transient ischemic attacks with the use of four aspirin a day, the benefit, which was for men only, was at best modest. The expectation of developing more effective and specific treatment to prevent strokes has dovetailed with research on the pathophysiology of platelets, coagulation and prostaglandins. Prostaglandins are inhibited by aspirin, but two prostaglandins are crucial in platelet aggregation. Prostacyclin, which is synthesized in vessel walls, is a powerful antiaggregant and is opposed by thromboxane A_2, a potent platelet aggregant that is synthesized in the platelets. Low-dose aspirin therapy preferentially interferes with function of thromboxane A_2, which reduces the likelihood of platelet aggregation. Adenosine diphosphate plus thromboxane A_2 are two potent platelet aggregants; therefore, inhibition of adenosine diphosphate secretion with dipyridamole may be synergistically effective.

Ongoing collaborative studies by Fields and co-workers on combination therapy using aspirin (one 320-mg tablet four times a day) plus dipyridamole (75 mg four times a day) and by Bousser and associates in Paris should shed light on this problem. Furthermore, more specific agents that will directly affect the prostaglandins show promise of even greater effectiveness.

While awaiting the results of clinical trials and newer drugs, the following medical therapy for transient ischemic attacks of the brain can be recommended: low-dose aspirin (one 320-mg tablet a day) and dipyridamole (50 mg three times a day).

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Treatment of Febrile Convulsions

THE MANAGEMENT of febrile convulsions must be based on both a clear understanding of the natural history of the disease and the risks and benefits of treatment. Febrile convulsions affect 5 percent of children in the United States, with the peak age of susceptibility being between 9 and 20 months. The sequelae of febrile convulsions have been reported to include death, hemiplegia, epilepsy and intellectual impairment. However, a number of both prospective and retrospective studies involving large numbers of patients have suggested that serious sequelae are rare. For example, in a recent study of 1,706 children with febrile seizures there were no deaths and no persisting hemiplegias. Moreover, large groups of cases with a primary diagnosis of febrile convulsions have been followed for up to 20 years and in only 1 percent to 4 percent has epilepsy been reported to develop.

The most frequent sequel of an initial febrile seizure is another febrile seizure because approximately 30 percent of untreated children have at least one recurrence. The best predictor of recurrence is early age at onset. Therefore, children whose first seizure occurs before they are a year old should receive prophylactic medication. It has also been proposed that all children should be treated after a second seizure.

The major goals of chronic anticonvulsant treatment of febrile seizures are the reduction of recurrence and the prevention of afebrile convulsions. Considering the relatively benign nature of most febrile convulsions and the risks inherent in chronic prophylaxis, it seems prudent to identify a subset of children for whom treatment would be recommended. In a recent National Institutes of Health collaborative study, three risk factors were identified that correlated with an increased risk of epilepsy developing; a family history of afebrile seizures; a preexisting neurological abnormality, and a "complicated" initial seizure—that is, one lasting more than 15 minutes, recurring within 24 hours or having focal features. The relatively high-risk group with two or more risk factors deserves consideration for prophylactic anticonvulsant treatment.

Regular prophylaxis with phenobarbital or valproic acid given in adequate doses can decrease the frequency of recurrent febrile convulsions by approximately half. However, there is no evidence that prolonged anticonvulsant therapy prevents the development of epilepsy or significant neurological deficits. Side effects or toxic reactions to phenobarbital, including behavioral changes and sleep disturbance, develop in up to 40 percent of children. Valproic acid has fewer side effects, but the rare case of toxic hepatitis can be life-threat-

ening. Liver function tests should be done when this medication is prescribed and, whenever chronic prophylaxis is undertaken, blood levels should be monitored and drug concentrations kept within therapeutic range. Diphenylhydantoin therapy does not prevent recurrence in children younger than 3 years, and intermittent medication is of no benefit. There is no consensus about how long to continue treatment, some authors suggesting until 4 years of age or after one seizure-free year, whichever is later. Parent education both about the nature of the illness and possible side effects of medication is the most important factor in maintaining compliance.

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The Role of Valproic Acid in the Management of Seizure Disorders

VALPROIC ACID (Depakene) was approved for use in the United States as an anticonvulsant in 1978. Subsequent experience with this medication indicates that it is a useful therapeutic agent for several types of seizures but also has significant toxicity.

Valproic acid appears to be more effective for treating generalized than focal types of epilepsy. In several large series, between 50 percent and 75 percent of patients taking this medication had at least 75 percent improvement in seizure control. Patients who have petit mal epilepsy (absence seizures) respond best to valproic acid, though patients who have atypical absence, myoclonic and generalized tonic-clonic seizures also respond well. Infantile spasms and akinetic seizure disorders are minimally affected by valproic acid.

Although it has significant side effects, valproic acid is a useful anticonvulsant medication, especially in refractory cases of generalized seizure disorders. The initial dosage is usually 250 mg four times a day in adults and 15 to 20 mg per kg of body weight a day in children, after which the dosage is adjusted to achieve a blood level of 50 to 100 μg per ml. Valproic acid has a relatively short half-life (6 to 15 hours) and is thus given in several doses a day. Some centers, however, have reported improved seizure control with once or twice a day administration. Valproic acid administration increases serum concentrations of phenobarbital and decreases phenytoin concentrations, so that blood concentrations of these medications should be monitored closely when used in combination with this drug. Complete blood counts, platelet counts and liver function tests (determining ammonia content may be especially helpful) should be checked at about two- to three-month intervals while a patient is taking valproic acid.

Despite initial reports of low toxicity, several major adverse effects have been described. At least 50 reports of fatal hepatic necrosis have appeared in this country since 1978. In these cases there does not appear to be a clear relationship between the hepatic disorder and dosage, duration of time taking valproic acid or serum aspartate aminotransferase values. Withdrawal of the drug after symptoms appear has not always led to reversal of the problem, and some patients have later died of liver disease despite drug withdrawal early in the course. Acute pancreatitis, in at least one instance, has also been reported to occur in association with valproic acid use. Less dangerous side effects include gastrointestinal disturbances (nausea, vomiting, diarrhea and changes in appetite), which occur in as many as 45 percent of patients. Alopecia (usually mild) has been found in 0.5 percent to 4 percent of patients. Valproic acid inhibits the second phase of platelet aggregation and may produce clotting abnormalities. Thrombocytopenia has also been reported rarely.

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Gilles de la Tourette's Syndrome

GILLES DE LA TOURETTE'S SYNDROME (GTS) is a disorder consisting of multiple motor tics and vocalizations, which begins in childhood or early adolescence. Coprolalia, the involuntary utterance of obscenities, long considered to be pathognomonic, is present in less than half of patients. Related features such as echolalia, palilalia and compulsive behaviors are not always present but help to clarify the diagnosis when they are. The clinical course characteristically waxes and wanes.

The lack of neuropathological findings in GTS

has led to an array of psychological explanations of the unusual characteristics. Shapiro and associates established GTS as a neurologic disorder with an increased incidence of sinistrality, generalized electroencephalographic abnormalities, neurological soft signs and organic indices found on psychological testing. The response of the tics to haloperidol suggested that GTS is a disorder of central dopaminergic activity. With the introduction of clonidine (a presynaptic α_2-noradrenergic agonist) for the treatment of GTS (Cohen and coworkers 1980), an alternative pharmacologic approach became available that focused attention on noradrenergic systems.

Behavioral features including hyperactivity, impulsivity, compulsivity, irritability and a low frustration tolerance have recently been emphasized. Shapiro and colleagues reported that more than half of their GTS cases met criteria for a diagnosis of hyperkinetic syndrome (minimal brain disturbance, now called attention-deficit disorder). Other features such as obsessive-compulsive behavior are less universally accepted but appear to be increasingly prevalent in GTS.

Clonidine may most beneficially affect the behavioral abnormalities, whereas haloperidol affects the tics. Because of the overall lower incidence of significant side effects, clonidine has been useful in treating patients who are unresponsive to or who cannot tolerate the side effects of haloperidol. A combination of the two drugs often produces beneficial effects, even when both drugs are given in lower doses than is useful if either is given alone. Experimental treatments using drugs that exert their primary effects on cholinergic and γ-aminobutyric acid-aminergic systems have met with limited success.

Two new syndromes related to GTS have been described. *Toxic Tourette's syndrome* is the development of GTS in children treated with stimulant medications for hyperkinetic syndromes. It is unclear whether these medications cause expression of an underlying predisposition toward the development of GTS. Because the syndrome is irreversible in some patients, even when the medications are withdrawn, caution is advised in the use of these agents.

Tardive Tourette's syndrome describes the development of a GTS-like disorder in patients exposed to high doses of neuroleptic medication for several years. Most patients with this syndrome have been schizophrenic.

Gilles de la Tourette's syndrome should be viewed as a "pervasive neuropsychiatric" syndrome with motor and behavioral features, both of which should be considered in the evaluation and treatment of the disorder.

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Neurologic Complications of Routine Immunization

COMPLICATIONS FOLLOWING IMMUNIZATION have been described at each anatomic level of the nervous system: peripheral nerve, nerve root and nerve plexus, spinal cord and brain. Awareness of these complications will aid a physician in the diagnosis and treatment of many unexplained acute neurologic problems following immunization.

A disorder of distal peripheral nerves resembling carpal tunnel syndrome has been described following rubella immunization. Clinically patients have intense pain at the wrist (and sometimes the knee), occasionally bilaterally, with pain most severe at night. Latency of onset is 10 to 70 days, with a mean of 45 days, after immunization. Electrophysiologic studies show slowed median nerve conduction velocity and prolonged median nerve motor and sensory distal latency. This syndrome resolves completely without any specific therapy usually within a month.

Brachial plexopathy has occurred following immunization. Peak incidence of occurrence is usually two to three weeks after immunization. Administration of tetanus toxoid or horse tetanus antitoxin is occasionally asssociated with this complication. This syndrome is often heralded by intense pain in the shoulder, arm and hand, but most patients recover completely. Treatment with steroids has not been provèd effective.

Guillain-Barré syndrome has been linked epidemiologically to the A/New Jersey (swine flu) National Influenza Immunization Program of 1976. The peak period of increased risk was within five weeks of immunization, and lasted for up to ten weeks. Subsequent influenza immunization programs have not been associated with increased risk of Guillain-Barré syndrome.

The spinal cord is sometimes involved follow-

ing routine immunization. Rarely, orally given live polio vaccine (OPV) has caused acute poliomyelitis. This disorder occurs in both vaccine recipients and their contacts. The risk is estimated at 0.06 cases per million doses for recipients of OPV and 0.14 per million for contacts. There is an increased risk of vaccine-induced poliomyelitis in adults (older than 18 years) receiving OPV. (There is no risk of poliomyelitis developing from inactivated polio virus vaccine.) The interval between immunization and onset is one to four weeks and clinically it is essentially the same as naturally occurring poliomyelitis.

Encephalopathy, sometimes with permanent neurologic sequelae, is a rare complication of routine pertussis immunization. Estimate of the rate of serious central nervous system complications occurring with residual deficit is about 1 per 510,000 vaccinations, though the incidence of transient convulsions or shock may be as low as 1 per 3,100. There is no evidence that a preexisting neurologic deficit is a contraindication to pertussis immunization unless, of course, the deficit was due to a previous pertussis immunization. Neurologic reactions to pertussis vaccine occur soon after vaccination, often within 1 to 48 hours.

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EDITORIALS

Thoughts on the Past, Present and Future of *WJM*

At a recent meeting of the Editorial Board there was earnest discussion not only of the format and content of the journal, but of its present and future role in the expanding universe of medical journals and particularly of specialty journals. The fact is that The Western Journal of Medicine is now becoming recognized as a genuinely representative regional medical journal and that it has a growing national and even worldwide audience. Its circulation is increasing in a healthy fashion. Therefore it seems most appropriate at this time to take a moment to reflect upon where the journal has been, where it is and where it might be going. These are some of the thoughts of the editors.

The early roots of the journal are to be found in the *Transactions of the Medical Society of the State of California,* which were published annually from 1873 until 1901. In 1902 *The California State Journal of Medicine* was established as a monthly publication by the Medical Society of the State of California. Under one name or another this medical journal has been in continuous publication ever since. An editorial note in the first issue in November 1902 stated "In addition to the official reports of the annual meetings of the State Society, and the papers and discussions of the scientific section, the Journal will publish a limited number of original articles, reports of county societies, and such other matters as may be of interest." This set the pattern that the journal was to follow for more than 50 years. In 1924 the name was changed to *California and Western Medicine* and in 1946 under the editorship of Dwight L. Wilbur it became *California Medicine.* Its past is therefore an honorable one, beginning as a record of the transactions of a state medical society and in 1902 being reborn as an educational benefit for the members of a growing and progressive state medical association.

The present may be said to have begun in 1967 when Dr. Wilbur, as retiring editor, suggested that the journal should become of "real scientific stature" and should seek to become a regional and then a national medical journal to reflect the growing scientific, social, economic and political progress of medicine in the West. The Council of the California Medical Association agreed, and the new editors accepted these goals for the journal. In 1974, by action of the CMA Council, it became The Western Journal of Medicine, and it is now, by action of each state's House of Delegates, the official journal of seven Western state medical associations and has paid subscriptions from each of the 50 states and many foreign countries as well. The circulation has now grown to more than 46,000 copies each month.

A journal with expanding horizons such as these and with great hopes for the future should, and indeed must, be useful to its readers if it is to succeed. The present editors have sought to make this a most useful journal, as well as one of the highest scientific quality. Mindful that our readers are mostly physicians in practice, but also include medical students, residents, educators, medical investigators, and important leaders in academic and organizational medicine, the editors have attempted to provide something in each issue that could be of use to any or all of these. The journal has therefore sought to help each reader to become knowledgeable about progress in medical science and problems in medical practice and patient care, not only in his or her own area of special interest but in other areas of general medical interest that may impinge upon any practice. To do this it has

made a point of cutting across specialty lines. In no way does *WJM* expect to compete with specialty journals, but it does expect over time to reflect important progress in each of the specialties. In addition the journal on occasion seeks to transcend the specialties in order to call attention to a broad range of issues, ideas and subject matter that are important to the practice of medicine and therefore to all physicians. In these ways it strives to be useful to all its readers, no matter what their particular interest or specialty.

The goal, then, has been a balanced fare for the education, enjoyment and profit of each of its readers. A perusal of this or any issue of the journal will show its regular features which include original articles (usually scientific), medical progress review articles (started in 1964), medical staff conferences (started in 1966), specialty conferences (started in 1969), epitomes of progress (started in 1970 and prepared by the specialty Advisory Panels of the Scientific Board of the CMA), case reports, editorials (usually two invited scientific editorials directed to articles in the current issue, plus one or two on nonscientific subjects usually of medical socioeconomic interest), items of information and correspondence. Features appearing intermittently include book reviews, clinical notes and such topics as community medicine, ethical issues, environmental health, government and medicine, medical economics, medical education, medicine in society, medicine in perspective, professional liability and special articles of particular interest. Occasionally, perhaps once or twice a year, a whole issue or part of one is devoted to a broad consideration of a special subject, the most recent of these being an entire issue devoted to geriatric medicine in December 1981.

The editors continue to seek ways to improve the scope, usefulness and scientific quality of the journal. In the near future a special editor named by the Intersociety Council (a consortium of five western scientific societies) will encourage the submission of original scientific articles of high quality and clinical interest to THE WESTERN JOURNAL OF MEDICINE. This should further enhance the scientific stature of the journal. A series of articles on primary care dealing with topics useful to physicians in daily practice, but not usually addressed in journals of scientific stature, has recently been instituted. In addition contributions are expected soon from the public health officers in the Western states which it is hoped will deal with topics of scientific and practical interest to readers throughout the West and elsewhere.

The journal has therefore progressed from merely a record of the transactions of a state medical society to a state medical journal of genuine distinction to, now, a journal that seeks to bring awareness of the progress and problems of all of medicine to a broadened scope of readers who live and work in many states and in many practice settings in the West and elsewhere. The present approach and general format may be expected to continue. But when one attempts to look ahead one senses that medical science and medical practice are destined to take on new and as yet unimagined dimensions. There will surely be enormous further advances in medical science that will have as yet unpredictable effects on the art and science of patient care. Medicine and health care will surely become ever more closely interwoven in the social, economic and political fabric of society, and much of the leadership for the cutting edge of progress and change is likely to come from the West. Just as in its present phase the journal is trying to provide its readers with awareness of the whole of medicine by crossing specialty lines, the future may see it also striving to provide them with an awareness of entirely new dimensions of health science and health care that are certain to develop and that may also be expected to transcend specialty lines.

In its future, as in its past, *WJM* should grow in excellence, usefulness and readership. In the process it should continue to offer its readers a balanced summary of the changes in medical science; the changes in social, economic and political attitudes, and the resulting changes in contemporary approaches to sickness, health and health care. THE WESTERN JOURNAL OF MEDICINE should strive always to be an authoritative, readable journal of recognized scientific excellence which will reflect the energy and progress of the West in medical science and in the technologic, social, economic and political ramifications of this progress in health care. In the process it should always be attentive to the needs of busy practitioners, medical students, residents, educators, researchers and important leaders in academic and organizational medicine. Its star should be a bright one in the universe of medical journals and professional publications.

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NMR: Diagnostic Wave of the Future

SINCE ITS DISCOVERY in the 1940's, nuclear magnetic resonance (NMR) has been used by scientists to determine the molecular structure of chemical specimens. But only recently has NMR been applied to study the biochemistry of intact organs and to image various parts of the body. Despite the newness of the technology to medicine, applications foreign to existing technologies are already evident. By depicting the concentration, chemical form and spatial distribution of sensitive atomic nuclei, NMR is able to define body constituents and chemistry directly but noninvasively. Existing diagnostic technology defines structure (ultrasonography and radiography) or relies on injection of foreign substances to evaluate function or metabolism (angiography and radiotracer studies). With the use of NMR, atomic nuclei and chemical species can be studied directly. Thus, inferences about tissue health need not be made by looking at indirect functions such as radiographic attenuation or radiotracer distribution. Moreover, it is possible that NMR approaches will create an even greater diagnostic window by eliciting information analogous to that obtained by radiographic and radiotracer means through the use of metabolic or flow "tracer" chemicals.

The diagnostic potential of NMR is shown in part by a brief description of a few of the medically relevant sensitive nuclei: phosphorus 31, sodium 23, carbon 13 and hydrogen 1 (proton). ^{31}P, ^{23}Na and ^{13}C all have NMR sensitivities many times less than hydrogen. In vitro, ^{31}P NMR spectroscopy has been used to monitor the concentration of adenosine triphosphate, creatine phosphate and inorganic phosphate.[1] Each phosphate has a characteristic spectral position separate from the others. This separation is referred to as a chemical shift. With in vitro spectroscopy studies such as NMR it is possible to directly evaluate high-energy phosphate metabolism. In addition, the chemical shift position of the inorganic phosphate peak is related to pH and can be used to measure intracellular pH. Recently, Brown and co-workers[2] reported the feasibility of imaging chemical shift phosphate peaks in biologic concentration. In this way NMR can provide in vivo assessment of the effect of disease on intracellular biochemistry.

Sodium is abundant in extracellular fluid. Because of the substantially higher concentration of sodium in blood compared with its concentration in cells, sodium may be useful as a "blood pool" imaging agent. In fact, DeLayre and associates[3] recently published gated cardiac blood pool images of an isolated perfused beating rat heart using a spectrometer modified to produce images. Also, it is possible that intracellular leakage of sodium associated with damage to the cell membrane could be detected by NMR.

In contrast with ^{31}P and ^{23}Na, which represent nearly all of the phosphorus and sodium found in nature, ^{13}C represents only 1 percent of natural carbon. As such, it may be useful as an NMR tracer for evaluation of perfusion and metabolism. For example, precursors tagged with ^{13}C can be used to trace hepatic glycogen metabolism.[4]

The connection between the laboratory work and clinical application may be made by either topical magnetic resonance (TMR) or imaging. TMR is a highly innovative approach that generates NMR spectra of sensitive nuclei in intact animals or in humans. In TMR a spectrum is derived by isolating a sensitive volume in the object being investigated. For example, Ross and colleagues,[5] using a forearm in human volunteers and in patients with McArdle's syndrome, did studies with TMR to evaluate phosphorus metabolism during aerobic and ischemic exercise. Intracellular pH determined from chemical shift analyses of the inorganic phosphate peak paradoxically rose during ischemic exercise, due to the suspected inability of the metabolism of patients with McArdle's syndrome to break down glycogen. Other interesting applications of TMR have been investigated by Radda and his colleagues.[6]

While NMR spectroscopy with in vitro and TMR approaches provides a new way of studying disease, NMR imaging can depict location and concentration of sensitive nuclei. Protons are thus far the only nuclei that have been used in intact animals and in humans to produce images. The reason is twofold. First, protons are abundant in tissue water. Second, protons are the most sensitive nuclei for NMR detection. The state of the art in proton imaging is presented in an excellent review in this issue by Davis and co-workers. Proton images mostly depict water distribution.

Since Lauterbur in 1973[7] recognized that images could be derived from NMR by encoding

spatial information using a magnetic field gradient, rapid advances have led to the ability to produce tomographic or three-dimensional images with resolution rivaling x-ray computerized tomography. In contrast with radiography, the intensity of proton NMR images is largely related to the concentration of protons in water and lipids. In addition, relaxation times (T1 and T2) can be emphasized on NMR images by manipulating the timing of the radiofrequency pulses.[8] These "relaxation times" are affected by the chemical environment and may provide additional clues to the presence of disease. For example, work at the Massachusetts General Hospital using an ischemic stroke model in cats showed that changes in the NMR image occur as early as two hours after ligation.[9] Other important potentials of proton NMR imaging include the ability to depict blood flow patterns and the application of contrast-enhancing agents, such as paramagnetic molecular oxygen.

The progress from Lauterbur's concept in 1973 to proton images of high quality in 1982, coupled with the development of TMR, suggests a progression ultimately to methods that allow in vivo mapping of biochemical markers of cellular disease such as the measurement of high-energy phosphate levels, intracellular sodium pools and NMR tracers labeled with ^{13}C. For NMR to achieve its full potential, there will have to be an alliance between technologic and medical research and among pathophysiologically, biochemically and structurally oriented practitioners. Indeed, the level of advancement that is necessary for knowledgeable NMR research and practice could lead to the evolution of a new discipline in medicine.

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Poison Control Centers—A Vital Community Resource

On July 14, 1981, the state of California began spraying malathion over a wide area of northern California; on August 10, 1981, some 5,000 South San Francisco residents were evacuated after a silicon tetrachloride gas line ruptured; on September 2, 1981, there were 60,000 residents evacuated from downtown San Francisco after a polychlorinated biphenyl/methane gas explosion; on December 4 seven Laotians ate *Amanita phalloides* in Santa Rosa, California. In each of these toxic, or potentially toxic, circumstances, the San Francisco Bay Area Regional Poison Control Center was a focal information center for citizens, public and private agencies and the news media. These events vividly illustrate the expanding role of a poison control center and the importance of such a center as a vital community health resource.

Pediatricians and local health departments began organizing poison control centers in the early 1950's. These early centers attempted to provide information and referral as well as preventive programs for poisoning. Lovejoy and his colleagues[1] from Boston summarized the growth of poison centers in 1979. The experience of the Massachusetts Poison Control Center emphasized the importance of establishing regional poison control services in many states and showed that 45,000 calls handled during 1978 cost $4 a call and were cost effective in decreasing the number of emergency room visits.[1]

It is estimated that there are approximately 5 million accidental and deliberate poisonings per year, with approximately 5,000 deaths. As an accidental cause of death, poisonings are surpassed only by motor vehicle accidents, drowning and burns.[2] The expanding poison center activities provide vital links for health care services. There are currently some 650 poison centers in the United States, which are unevenly distributed. In California there are now three centers certified by the American Association of Poison Control Centers (Sacramento, San Diego and San Fran-

cisco) providing unique expertise in their geographic areas. The San Francisco Bay Area Regional Poison Control Center, reviewed in this month's issue, makes an important contribution in disaster planning and coping with hazardous spills and occupational health problems.

Many benefits from poison control activities are evident. Toxicity information relayed by the poison control center is well received by health professionals and patients. Vital links between physicians, nurses, pharmacists, toxicologists and the community are forged on important environmental and toxicologic issues. Data collection in local communities allows for epidemiologic studies of toxic events. Special hazards with new drugs or packaging and labeling of toxic chemicals are more easily recognized. Unusual health problems such as epidemic mushroom poisoning can be recognized and prevented. Public reassurance via telephone consultation when there is little or no hazard provides cost-effective medical care.

Some problems remain as poison control centers evolve as community resources. There are far too many centers that lack quality control. Major gaps exist in important toxicologic information that will require new research strategies. There are internal conflicts in professional organizations concerned with poison control centers. Perhaps the most pressing problem involves maintaining stable funding resources for this cost-effective service for which no appropriate billing mechanism has been found. Departments of public health, emergency medical services systems and local professional organizations share a major responsibility in maintaining the funding for these activities.

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CASE REPORTS

Refer to: Mecikalski MB, Depner TA: Peritoneal dialysis for isopropanol poisoning. West J Med 1982 Oct; 137:322-325

Peritoneal Dialysis for Isopropanol Poisoning

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LITTLE ATTENTION has been given in recently published work to the toxicology and clinical features of isopropanol poisoning. Also, isopropanol intoxication has been successfully treated with hemodialysis,[1,2] but there has been little assessment of the effectiveness of peritoneal dialysis.[3] Because peritoneal dialysis is more readily available and easily administered, we report the peritoneal and total body clearance determinations of isopropanol during dialysis of a child who accidentally ingested this toxic alcohol. Following is a brief review of its toxic effects and metabolism.

Report of a Case

An 18-month-old male infant was admitted to hospital comatose. Earlier in the evening his babysitter saw him drink from a bottle of rubbing alcohol (70 percent isopropanol). The estimated volume ingested was 2.4 dl (8 oz). He vomited shortly afterward, appeared intoxicated and was taken to a community hospital emergency room where he was noted to be stuporous and having labored respirations. After vomiting again he was given naloxone hydrochloride, 0.2 mg intravenously; an endotracheal tube was placed and the infant was transferred to the University of California Davis Medical Center where he arrived three hours after drinking the rubbing alcohol.

His temperature was 36°C (96.8°F), pulse 124 per minute and blood pressure 90/40 mm of mercury. His weight was 9.5 kg (21 lb). He had no spontaneous respirations, did not respond to verbal or painful stimuli, and made no voluntary movements. Pupillary, corneal and gag reflexes were absent but deep tendon reflexes were normal.

Laboratory studies disclosed the following values: serum sodium 136, potassium 3.6, chloride 111 and bicarbonate 12 mEq per liter; blood urea nitrogen 23, glucose 276, acetone 51 and isopropanol 272 mg per dl. Arterial blood gas determinations done while the patient was receiving 100 percent oxygen via a respirator were as follows: oxygen partial pressure 396 mm of mercury, carbon dioxide partial pressure 28 mm of mercury and pH 7.29.

Treatment initially consisted of 20 mEq of sodium bicarbonate given intravenously and gastric lavage with a 0.9 percent saline solution until fluid returned clear, followed by administration of charcoal and magnesium sulfate. Because of the initially high isopropanol concentration and profound neurologic depression, peritoneal dialysis was started two hours after admission (five hours after ingestion). A standard commercial dialysate (Travenol) containing 132 mEq of sodium, 4.0 mEq of potassium, 106 mEq of chloride, 35 mEq of lactate, 3.5 mEq of calcium and 1.5 mEq of magnesium per liter and 1.5 mg of glucose per dl was cycled in 1,000 ml volumes every 30 minutes. A total of 13 cycles were run during 6½ hours. The subsequent clinical course correlated with blood and dialysate toxin levels is shown in Table 1. Isopropanol and acetone concentrations were measured with a Carle 211 analytical gas chromatograph by an established method.[4] Urine output was 170 ml from admission to the discontinuation of dialysis. Following dialysis the infant's weight was 9.4 kg and the serum creatinine level was 1.5 mg per dl, falling to a baseline of 0.5 mg per dl the following day.

Extubation was carried out 24 hours after admission, but it was necessary to reintubate due to upper airway edema. The second and final extubation was done a day later. Developmental assessment during this hospital stay showed a return to normal function. The total length of time in hospital was 12 days.

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TABLE 1.—*Summary of Clinical Recovery and Corresponding Levels of Isopropanol and Acetone in Blood and Dialysate*

Time After Ingestion (hr)		Isopropanol			Acetone		
		Blood (mg/dl)	Dialysate (mg/dl)	Peritoneal Clearance (ml/min)	Blood (mg/dl)	Dialysate (mg/dl)	Peritoneal Clearance (ml/min)
0	Ingestion	..	..	..	..	.	..
3	Admission, comatose, no pupillary reflex, respiration or movement	272	..	..	51	.	..
5	Dialysis started	..	..	..	.	.	
5½		..	33	..	.	22	..
6½	Pupils sluggishly reactive	..	..	..	.	.	
8		62	19	10.2	75	30	13.7
9½	Spontaneous respirations, able to be aroused	..	..	..	.	.	
10½		27	7	8.6	80	31	12.9
11	Limb restraints necessary	..	..	..	.	..	.
11½	Dialysis discontinued	..	..	..	..	.	
14½	Making purposeful movements	<5	..	..	91	..	

Discussion

Although about 10 percent of isopropanol may be converted to the glucuronide,[5] the major pathway of metabolism is via alcohol dehydrogenase to acetone.[6] A case of a confused or comatose patient having acetonuria in the absence of glycosuria, especially without evidence of starvation, should suggest a toxic reaction to isopropanol. An unexplained rise in serum osmolality may call attention to the presence of a foreign substance, and might be used as an estimate of isopropanol concentration if an accurate assay is not available and if it is certain no other substance has been ingested. Acetonemia may reach significant quantities[1,3] and exacerbate a toxic condition, as its effects are similar to ethanol at equal blood concentrations.[7,8(p123)] Its rate of metabolism is much slower, however,[7,9] which probably accounts for the continued slow increase in blood acetone content in this patient even though blood isopropanol content was decreasing. This behavior of isopropanol and acetone concentrations has been seen in experiments with animals.[6,9]

Isopropanol quantities in body fluids are best measured by a gas chromatographic method. Users of alcohol dehydrogenase testing methods may be misled by ethanol[10] and earlier researchers using a modification of an iodometric assay for ethanol may have been misled by acetone.[11] In most cases of toxic ingestions in which coma occurred, blood concentrations were greater than 125 mg per dl,[1,2,12-15] with some patients who died having measurements at 150 mg per dl.[16] One infant survived, receiving supportive therapy alone, with a level of 520 mg per dl.[12] It must be noted that the methods used to assay for isopropanol were not specified in any of these reports nor were acetone levels routinely measured.

The volume of distribution of isopropanol is 0.7 to 0.8 times body mass, similar to ethanol.[17,18] The rate of metabolism of isopropanol is proportional to its concentration and follows simple first-order kinetics.[9] This contrasts with ethanol which saturates its metabolic mechanisms at very low levels and therefore usually declines at a linear rate independent of concentration.[19]

The blood content of isopropanol given in Table 1 follows an exponential rate of decline, with an elimination constant during dialysis of 33 percent per hour. Assuming a volume of distribution of 7.1 liters the total body clearance of isopropanol during dialysis is 39 ml per minute to which peritoneal dialysis contributes 9.4 ml per minute or approximately a fourth. The non dialysis or metabolic elimination constant is 25 percent per hour and compares favorably with previously reported values for dogs and rats of 17 percent and 35 percent per hour respectively.[9] Assuming these clearances and the volume of distribution of isopropanol to be constant, the blood concentration at the start of dialysis can be estimated to be 167 mg per dl and the maximum level before admission to be about 400 mg per dl. The latter quantity correlates with the profound degree of neurologic depression we observed.

Isopropanol is most widely encountered in a 10 percent solution sold as rubbing alcohol, but it may also be found in cosmetics, mouth washes, hair tonic, skin disinfectants, deicers, antifreeze and solvent mixtures.[20] Absorption from the gut is rapid and complete. Using isolated segments of

gastrointestinal tract from dogs, Wax and coworkers[21] determined the absorption of a dose of 1.25 ml per kg of body weight (as a 10 percent solution) in stomach, duodenum and jejunum to be 41 percent, 67 percent and 91 percent, respectively, at 30 minutes. In jejunoileal loops absorption was 99 percent complete in two hours.

Symptoms and signs of a toxic reaction to isopropanol are generally similar to those seen with ethanol, though isopropanol probably does not produce an initial stage of stimulation.[20] Symptoms of a toxic reaction include dizziness, incoordination, headache, confusion, stupor, coma, hypothermia, aspiration and respiratory arrest. Gastroenteritis, more prominent than that usually seen with ethanol poisoning, may occur.[8(pp185-188)] Hypotension is a bad prognostic sign.[16] Renal failure has been reported possibly as a result of hypotension[16,22] or rhabdomyolysis.[23] Postmortem studies have shown hemorrhagic gastritis, hemorrhagic tracheobronchitis and pulmonary edema but no specific changes.

Studies with animals have shown that isopropanol is about 1½ to 2 times as toxic as ethanol. The certain lethal dose for a 70-kg (154-lb) human would then be about 500 ml of pure alcohol or 25 oz of 70 percent rubbing alcohol.[24,25] In one study it was noticed that deaths from isopropanol occurred considerably later than those from ethanol.[25] Both death[16] and survival[23] have been reported with presumed ingestion of 4.7 dl (16 oz) of rubbing alcohol. Two cases of isopropanol poisoning have been described in infants receiving alcohol baths for fever.[13,14] The route of absorption was presumably inhalation as large amounts of isopropanol applied topically to animals have had little effect.

After gastric lavage it is reasonable to attempt to hasten recovery from isopropanol intoxication, especially in comatose or hypotensive patients, but the medical urgency is not as great as that for methanol intoxication where permanent neurologic damage may occur due to the production of formaldehyde and formic acid. Similarly, ethylene glycol, whose metabolite oxalic acid is very corrosive and a potential cause of renal failure, should be removed promptly. Ethanol, isopropanol and their metabolites have lower intrinsic toxicities than methanol and ethylene glycol metabolites. Supportive therapy rather than an attempt to promote active excretion may be adequate for the former substances, whereas rapid removal of methanol and ethylene glycol is much more important. Isopropanol poisoning alone probably is not alleviated by activated charcoal administration if its adsorption characteristics roughly parallel those of ethanol, which is adsorbed in amounts of about 0.5 gram per gram of charcoal.[26,27] Because relatively large amounts of these alcohols are necessary to produce toxic effects, the quantity of charcoal administered would have to be correspondingly great. It would also need to be administered soon after the alcohol ingestion, as isopropanol is absorbed so rapidly in the gut.

Hemodialysis has been shown to be effective for removal of both ethanol and methanol in humans and clearances have approached 150 ml a minute in vitro.[19] Limited studies have shown that hemodialysis is also effective in lowering blood quantities of isopropanol, which in turn accelerates recovery of intoxicated patients.[1,2] Urine levels of isopropanol closely parallel those in the blood,[1] indicating that it is not substantially concentrated in the urine and that forced diuresis would be relatively ineffective. As an example, a daily urine flow equal to the total body water volume would require about 16 hours to merely halve the initial isopropanol concentration.

In this normotensive patient who had no evidence of hepatic disease, peritoneal dialysis, though effective in removing isopropanol, accelerated endogenous removal rates by only 30 percent and contributed little to the observed decline in isopropanol concentration in urine. However, peritoneal acetone clearance was substantial, approximately equivalent to expected pulmonary clearance, and may have hastened central nervous system recovery.

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Hematologic Improvement Following Splenectomy for Hemoglobin-H Disease

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THE RECENT INFLUX of Southeast Asians into the United States has provided the American medical community with a host of unfamiliar medical problems, mainly hemoglobinopathies and infections. The patient in this report has a form of α-thalassemia, a hemoglobinopathy that is highly prevalent in Asia, having a frequency of 4 percent in China and 20 percent in Thailand.[1] The genetics and molecular mechanisms of α-thalassemia have been well reviewed.[1-7] Normally, the α-chain of the hemoglobin molecule has four α-globin structural genes $(\alpha\alpha/\alpha\alpha)$[8-10] that are located at two genetic loci.[11,12] Either gene deletion[8-12] or a dysfunctional nondeletion lesion[7,11,13] can result in a thalassemic α-globin gene. When only a single normal α-globin gene is present $(--/-\alpha)$ the clinical result is hemoglobin-H (HbH) disease, which is characterized by moderately severe hemolytic anemia, microcytosis and splenomegaly. A mutant gene coding for the elongated α-globin chain of the electrophoretically slowly migrating hemoglobin Constant Spring (HbCS) mimics a thalassemic α-globin gene in that HbCS is present in very low amounts.[14-16] Thus, the clinical syndrome of HbH disease is seen also with the presence of one normal α-globin gene and an α^{CS}-globin gene.[14] HbCS is found in 40 percent of Southeast Asians with HbH disease.[17]

Herein we report the case of a young Cambodian woman who underwent splenectomy resulting in successful relief of the symptoms of anemia due to HbH disease associated with HbCS. The anemia of HbH disease is related to decreased synthesis of α-globin and of total hemoglobin[18,19] and to hemolysis, a result of unbalanced globin synthesis,[20] that occurs mainly in the spleen.[21] Thus, the intent of splenectomy in this patient was to diminish the peripheral hemolytic component of the anemia. When last reviewed in the 1960's, the efficacy of this procedure was uncertain.[21,22-24] Accordingly, we did a complete hematologic assessment both before and after the operation to evaluate the patient's response to splenectomy.

Report of a Case

A 24-year-old woman who recently immigrated to this country from Cambodia was admitted to Highland General Hospital in July 1980 for evaluation of dizziness, weakness, dyspnea and dis-

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comfort in the right upper quadrant of the abdomen that had persisted for two months. The patient had been weak and sickly throughout her life. Shortly before her departure from a refugee camp in Thailand, she had onset of fever, dizziness, headaches and dyspnea on exertion. At the same time she had an episode of severe abdominal pain in the right upper quadrant that lasted several days. On arrival in the United States in April 1980, evaluation by the Public Health Service showed a positive tuberculin skin test with purified protein derivative and isoniazid therapy, 300 mg a day, was started. Hookworm and *Clonorchis sinensis* ova were found in a stool specimen; the hookworm infestation was successfully treated with chloroquine.

On physical examination the young woman was pale but otherwise appeared well. Her conjunctivae and nailbeds were also pale. There was no significant lymphadenopathy. Examination of the chest showed no abnormalities. On cardiac examination a grade 3/6 systolic flow murmur was noted, heard best at the base. There was mild tenderness in the right upper quadrant of the abdomen and a spleen tip was palpable.

For the next two months, the hemoglobin level ranged from 7.8 to 8.3 grams per dl, the hematocrit from 27.5 percent to 30.2 percent, the mean corpuscular volume from 69 to 71 cu μm, the mean corpuscular hemoglobin from 19.6 to 20.5 pg and the mean corpuscular hemoglobin concentration from 28.3 to 28.6 grams per dl (Table 1). The leukocyte count ranged from 6,000 to 9,000 per μl, with 5 percent to 8 percent eosinophils. Platelet count was 300,000 per μl and absolute reticulocyte count was 560,000 per μl. Results of a Heinz body preparation[25] were negative. Erythrocyte morphology was frankly abnormal due to basophilic stippling, target cells and teardrop forms. Brilliant cresyl blue preparation[21] showed the multiple small punctate inclusions typical of HbH disease (Figure 1). The total serum bilirubin level was 1.9 mg per dl and indirect bilirubin was 0.8 mg per dl. Serum haptoglobin concentration[26] was 10 mg per dl (normal, 60 to 270). Bone marrow was 90 percent cellular with an erythroid-to-myeloid ratio of 7:1, confirming the diagnosis of severe hemolytic anemia. Iron deficiency was ruled out by the finding of normal marrow iron stores. Hemoglobin electrophoresis of fresh blood on an alkaline starch gel (pH 8.6) showed a small amount (1 percent) of a slowly migrating band, a feature of HbCS, in addition to hemoglobins A, A_2 and H. α-Globin gene mapping by blot hybridization[11,27,28] showed α-globin genes at both loci, a result compatible with a genotype of $--/\alpha^{CS}\alpha$.

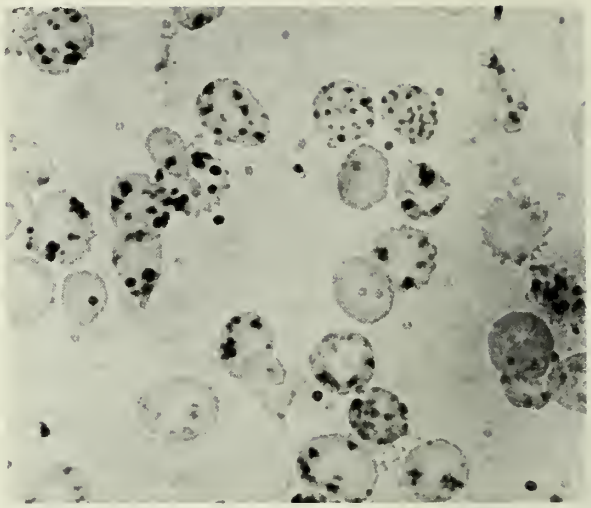

Figure 1.—Before splenectomy, erythrocytes show multiple punctate inclusions. Erythrocytes have been stained with brilliant cresyl blue supravital stain.

TABLE 1.—*Hematologic Values in a 24-Year-Old Cambodian Woman Before and After Splenectomy*

	Before	*After*
Hemoglobin (grams per dl)	7.8-8.3	9.0-9.6
Hematocrit (percent)	27.5-30.2	32.4-34.0
Mean corpuscular volume (cu μm)	69-71	68-71
Mean corpuscular hemoglobin (pg)	19.6-20.4	19.4-20.6
Mean corpuscular hemoglobin concentration (grams per dl)	28.3-28.6	28.4-28.6
Absolute platelets (per μl)	300,000	600,000
Absolute reticulocytes (per μl)	560,000	469,580

Thus, her HbH disease was the result of two α-globin genes deleted from one chromosome, one gene on the other chromosome producing low levels of the elongated α-chain of HbCS and one normal α-globin gene. Roentgenograms showed cardiomegaly and radiopaque gallstones. In view of the patient's symptomatic cholelithiasis and significant morbidity from anemia, cholecystectomy and splenectomy were done concurrently without complication in September 1980. The spleen weighed 250 grams.

Three months after the operation, the patient no longer had dizziness, dyspnea, weakness or other symptoms. Her hemoglobin level ranged between 9.0 and 9.6 grams per dl, hematocrit between 32.4 percent and 34.0 percent and erythrocyte indices and leukocyte count had not changed (Table 1). Absolute reticulocyte count

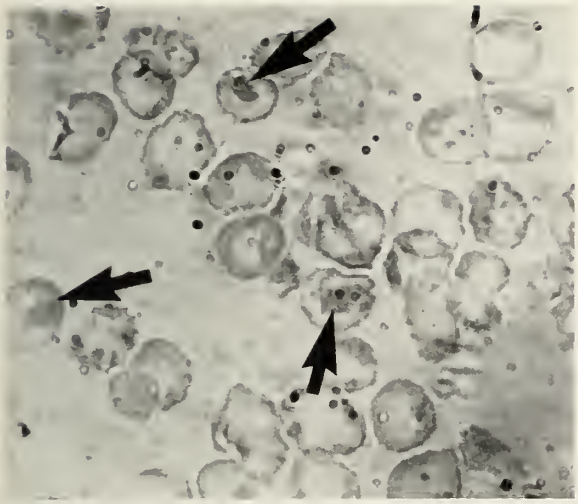

Figure 2.—After splenectomy, erythrocytes show occasional large single inclusions (arrows). Erythrocytes have been stained with brilliant cresyl blue supravital stain.

decreased slightly to 469,580 per μl. Platelet count rose to 600,000 per μl. Brilliant cresyl blue preparation showed the large single inclusions characteristic of splenectomized persons with HbH disease and the multiple small inclusions seen preoperatively (Figure 2).

Discussion

An abdominal operation was indicated for symptomatic cholecystitis and we recommended concurrent splenectomy for relief of the symptoms due to anemia. The anemia of HbH disease is related to impaired α-globin and hemoglobin production[18,19] and to hemolysis resulting from unbalanced globin synthesis.[20] The hemolysis occurs predominantly in the spleen and to a lesser degree in the bone marrow.[21,29,30] Intramedullary hemolysis plays a smaller role in the anemia of HbH disease than it does in β-thalassemia.[21,28,29] This difference is probably related to the greater solubility and more delayed precipitation of the excess β-chains in HbH disease compared with the less soluble, more rapidly precipitated excess α-chains in β-thalassemia.[30] The hematologic response to splenectomy in our patient appears to have been due to a decreased peripheral hemolytic component of this anemia.

Other articles regarding the efficacy of splenectomy for HbH disease contain conflicting opinions. Most reports suggest that splenectomy is beneficial[17,21-23] but one suggests that it is not.[24] We found no controlled studies and in some of the reported cases, a diagnosis of HbH disease was uncertain. In two cases in which splenectomy seemed beneficial, intestinal parasites were diagnosed and treated postoperatively, so it is uncertain whether the improved hematologic picture was due to splenectomy or to the eradication of the parasites.[21] The possible contributing role of iron deficiency to the anemia of HbH disease was generally not addressed in these reports. In the one case in which iron studies were reported, there was no element of iron deficiency and the splenectomy resulted in no improvement in hemoglobin levels.

Because the spleen is important in protecting against bacterial sepsis,[31-34] splenectomy should be done only for specific indications. Three months after eradication of intestinal parasites, our patient remained clinically impaired from the symptoms of anemia, so we proposed the option of splenectomy. Due to the absence of influences compounding her anemia, we believe that our patient's postoperative 1.5 gram per dl rise in hemoglobin level was attributable to the splenectomy. This result suggests a role for splenectomy in the management of HbH disease, but further experience is necessary to determine the widespread value of this approach.

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Aminophylline-Induced Exfoliative Dermatitis: Cause and Implications

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THE CLINICAL PHARMACOLOGY SERVICE was asked to evaluate the case of a patient with severe bronchospasm and a history of extensive exfoliative dermatitis after prior exposures to aminophyline. The medical team caring for the patient posed the following questions: Has this skin reaction to aminophylline been reported? Which component of the drug, theophylline or ethylenediamine, is more likely to be responsible? Is there any way the patient can safely receive any methylxanthine derivative?

Review of the *Physicians' Desk Reference*[1] and a standard pharmacology text[2] found only rare occurrences of urticaria, skin rash and pruritus had been reported as possible reactions to this drug. Contacting Searle Pharmaceuticals Inc. (Box 5110, Chicago, Illinois) did not elicit information on adverse reactions to Aminophyllin from (unreported) case histories of a similar skin problem. However, they were aware of one reference concerning a similar patient.[3]

A search of the industrial medicine and dermatology literature provided answers to the above questions. It was concluded that the patient was sensitive only to ethylenediamine (EDA), and he was challenged with anhydrous theophylline (Theo-Dur). He tolerated this well, and his bronchospasm improved. Thus the knowledge of EDA skin sensitivity becomes important to internists so as not to withhold the benefits of theophylline from similar patients.

Report of a Case

A 64-year-old man was admitted to hospital for increasing subacute dyspnea. He was in his usual state of compensated emphysema in which he had dyspnea on walking two city blocks, until a viral upper respiratory tract syndrome developed two months before admission. This progressed to bilateral pneumonia, diagnosed by x-ray studies of the chest. There was gradual improvement on a regimen of trimethoprim and sulfonamide. Two days before admission the patient noted severely increased shortness of breath at rest, wheezing and cough that produced thick, white sputum. The patient stated he did not have fever, chills, orthopnea, nocturnal dyspnea or other symptoms of infection or congestive failure.

The patient had a 100-pack-year history of smoking and during the last three years had been treated with terbutaline, 30 to 40 mg given by mouth a day, metaproterenol sulfate inhalant when needed and beclomethasone dipropionate inhalant intermittently. Three years before admission the patient had his first episode of bronchospasm and

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was treated with administration of aminophylline (intravenously, then orally) and tetracycline given by mouth for three days. On the fourth day, a severe exfoliative dermatitis developed. This responded slowly to oral and topical administration of steroids and discontinuation of aminophylline and tetracycline therapy. Several months later, severe bronchospasm again developed and his physician prescribed aminophylline, but warned against taking tetracycline because of the prior skin reaction. Ten hours later, after two doses, severe exfoliative dermatitis developed. Since then the patient had not received aminophylline or any other theophylline preparation despite intermittent episodes of bronchospasm.

Past medical history was remarkable for the fact that the patient had had severe eczema on his hands and ankles in 1945 and 1968, complicated by bacterial superinfection. On both occasions he received treatment with a variety of topical creams and ointments, including one cream containing both antibiotics and steroids. He worked as an accountant and had no prior occupational exposure to solvents, rubber, paint or varnish.

On physical examination the patient appeared nervous and was slightly obese and noncyanotic. Sitting up in bed, he was moderately dyspneic, using accessory muscles of respiration. He was afebrile and the pulse rate was 120 and regular, respirations were 36 and blood pressure 150/92 mm of mercury. On examination of the chest, diffuse wheezes were heard bilaterally, with prolonged expiration and no rales or rhonchi noted. Cardiac examination elicited distant heart tones but no abnormalities. The pertinent laboratory data derived on admission included x-ray studies of the chest, which showed no infiltrate, cardiomegaly or signs of congestive failure; a Gram stain of a sputum specimen showed rare granulocytes and small numbers of mixed flora, and arterial blood gas determinations made while the patient was breathing room air gave the following values: a partial oxygen pressure (Po_2) of 53 mm of mercury, a partial carbon dioxide pressure (Pco_2) of 36 mm of mercury and a pH of 7.43.

There was slight improvement on a regimen of chest physical therapy, inhaled isoetharine, methylprednisolone (125 mg given intravenously four times a day), terbutaline (10 mg given orally four times a day), oxygen and ampicillin (4 grams a day given intravenously). The patient's nervousness and urinary retention, which developed when the terbutaline dosage was increased to 40 mg a day, persisted. Closed patch tests were placed on the upper arm with aqueous solutions of 1 percent ethylenediamine dihydrochloride and 0.5 percent theophylline. Both skin tests were negative at 48 and 72 hours. A challenge test was then done with anhydrous theophylline (Theo-Dur), 100 mg given orally, and there was no skin reaction after 24 hours. Administration of theophylline was begun, therefore (200 mg given orally four times a day). Therapeutic serum concentrations were attained, and steady clinical improvement ensued. As the daily dose of terbutaline was decreased, the nervousness and urinary retention also decreased. The patient's discharge medications were as follows: theophylline, 200 mg taken by mouth four times a day; terbutaline, 5 mg taken orally three times a day; furosemide, 40 mg taken by mouth each day, and prednisone, 60 mg taken orally each day, and prednisone, 60 mg taken orally each day (to begin gradually tapering the dosage). He used his metaproterenol inhaler rarely, only when needed. The patient returned to the care of his private physician and was not available for follow-up patch testing.

Discussion

Ethylene amines can cause dermatitis, both irritative and allergic, and exposure to them has been associated with asthma in susceptible persons.[4-6] Ethylenediamine (1,2-ethanediamine), $C_2H_8N_2$, is widely used in industry for making dyes, fungicides, waxes, insecticides and resins; preparing casein, lacquer and shellac; as a stabilizer for rubber; a corrosion inhibitor in antifreeze; an acid neutralizer for oils, and in the manufacture and formulation of pharmaceuticals.[6,7] Ethylenediamine has increasingly become the cause of allergic contact dermatitis.[8-10] Eriksen[11] showed that EDA is a potent sensitizer in guinea pigs, corresponding to the clinical experience with humans.

When used in pharmaceuticals, EDA retains its property of being a sensitizing agent. In 1967 Provost and Jillson[12] reported on 13 patients over a four-month period who had contact dermatitis and positive patch tests to EDA. They had been using Mycolog cream (a mixture of triamcinolone acetonide, neomycin, gramicidin and nystatin), which contained EDA as a preservative. A few months later Epstein and Maibach[13] reported ten additional cases of such patients. Fisher and coworkers[10] included EDA on a "vehicle tray" for the patch testing of 100 patients who had contact dermatitis suspected to be due to topical medica-

tions. A total of 30 positive patch tests were obtained, 18 of these were to EDA.

Aminophylline consists of the methylxanthine theophylline and ethylenediamine in a molecular ratio of 2:1, with approximately 85 percent anhydrous theophylline and 15 percent EDA.[14] Because the solubility of theophylline is limited (less than 1 percent), the EDA is added to increase solubility, especially for parenterally administered preparations. Tas and Weissberg in 1958[15] described a 52-year-old pharmacist who prepared aminophylline suppositories and was found to have an allergy to aminophylline manifested by vesicular dermatitis, rhinitis and bronchial asthma. Patch tests to aminophylline and EDA were positive, but there was no reaction to theophylline. Six hours after inhalation tests with aminophylline and EDA, severe asthma developed and he had exacerbation of his skin condition. The next year Baer and colleagues[16] reported a similar case in a 58-year-old pharmacist with allergic eczematous contact dermatitis, who was patch test positive to store dust, aminophylline and EDA. The skin condition improved while he was in the hospital away from his store; subsequently he avoided aminophylline and had no recurrence of the skin problem.

In most cases the cause of exfoliative dermatitis is not known.[17] In a review article Adam[18] analyzed 176 cases; 10 percent of the patients probably had a drug-related condition. Petrozzie and Shore[19] reported the case of a patient with a past history of allergic contact dermatitis to Mycolog cream. Two days after subsequent exposure to aminophylline, generalized exfoliative dermatitis developed. Patch testing showed him to be highly sensitive to EDA, but not to the other components of Mycolog cream. It is well recognized that in persons sensitized by external skin exposure to a contact allergen, subsequent systemic exposure may produce a generalized skin eruption.[20]

Bernstein and Lorincz[3] reported the case of a 50-year-old woman in whom severe exfoliative erythroderma developed the day after she had been given aminophylline for an acute asthmatic episode. This resolved with discontinuation of the administration of that drug and topical steroids. Several months later she had a second episode of exfoliative erythroderma after an unintentional rechallenge with aminophylline given orally. After the skin lesions cleared, patch testing indicated a high degree of sensitivity to EDA and edetate (EDTA), but not to theophylline.

Lawyer and associates[21] studied a 37-year-old asthmatic woman in whom a generalized pruritic eczematoid dermatitis developed after three separate exposures to orally given aminophylline. Subsequent patch testing showed sensitivity to EDA. She later tolerated anhydrous theophylline (Theo-Dur) taken orally and intravenous administration of dyphylline (Neothylline) without any adverse effects. Such patients with known sensitivity to EDA should be instructed to avoid not only aminophylline, but other substances containing or derived from EDA, such as various antihistamines, Mycolog cream and Prefrin A eye drops (a solution containing pyrilamine maleate, phenylephrine hydrochloride, sodium bisulfite, sodium citrate, boric acid, edetate sodium, benzalkonium chloride and antipyrine).[20]

Summary

In answer to the medical team's questions, we conclude the following:

- The development of severe exfoliative dermatitis in this patient after exposure to aminophylline is similar to cases previously reported in the dermatology and industrial medicine literature, though not in the usual pharmacology reference sources.
- Although the patient's skin tests were probably confounded by the concomitant administration of high doses of steroids necessary for control of his bronchospasm, we believe his skin reaction was caused by EDA in aminophylline. The literature clearly indicates prior identical reactions to EDA, but no recorded cases of theophylline-induced exfoliative dermatitis.
- The patient was able to safely take anhydrous theophylline orally. If rapid intravenous administration of a methylxanthine ever became necessary, dyphylline could be used.[21]

Finally, whereas the incidence of aminophylline-induced exofoliative dermatitis seems to be quantitatively infrequent, it can be qualitatively severe when it occurs. Physicians confronted with this problem should be aware of the many medical preparations that contain or cross-react with EDA. Perhaps of greater importance, physicians should not deprive their aminophylline-sensitive asthmatic patients of theophylline itself, when ethylenediamine is responsibile for the sensitivity reaction. Theophylline in such cases may be safely given, thus improving the underlying condition and precluding toxic doses of other drugs.

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The Clinical Features of Covert Diuretic Use

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DIURETIC AGENTS are prescribed for the treatment of hypertension, congestive heart failure, hypercalciuria and edema. The side effects of these drugs are easily recognized when their use is known. However, covert diuretic ingestion can mimic a variety of disease states and patients may endure long, expensive and painful investigations rather than admit to medicine abuse.

We recently saw two patients who were surreptitiously taking diuretics. Their clinical features had led to previous investigations for hyperparathyroidism, sarcoidosis, cholelithiasis, Sjögren's syndrome, pancreatitis, renal insufficiency and Bartter's syndrome.[1] Workups had been inconclusive until laboratory test findings disclosed the presence of furosemide or thiazide, or both, in the urine of both patients. Despite denials of diuretic use, these drugs seemed to play a major role in the development of these patients' disease states. The cases are presented to alert physicians to the wide spectrum of presentations possible in patients abusing diuretics.

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Reports of Cases

CASE 1. A 29-year-old Native American woman was referred in July 1980 for evaluation of hypercalcemia and repeated bouts of pancreatitis.

In 1975 she had weighed 84 kg (185 lb). She lost 41 kg (90 lb) during the next three years with the use of diet and thiazide diuretics. She said she had not taken thiazides since June 1978. In April 1979 she complained of a dry mouth and arthralgias and underwent an evaluation for Sjögren's syndrome at a university hospital. The results of this evaluation were negative. Beginning in June 1979 repeated bouts of pancreatitis led to a gastrointestinal evaluation. Despite extensive investigations, including oral cholecystography and endoscopic retrograde cholangiopancreatography (ERCP), no cause for the pancreatitis was established. With the known high incidence of cholelithiasis in Native Americans, however, her repeated episodes of pancreatitis led to a cholecystectomy in August 1979. A normal gallbladder was found.

In September 1979, with a history of mildly elevated calcium and blood urea nitrogen (BUN) levels, she was examined for sarcoidosis and renal disease, with negative findings. In July 1980, due to mild hypercalcemia and persistent bouts of pancreatitis, she was referred to the endocrine

clinic for evaluation of possible hyperparathyroidism.

She was a thin, anxious young woman who had symptoms of thirst, nocturia, abdominal discomfort and malaise. She said she did not have diarrhea or vomiting or use diuretics or laxatives. She noted that hydrochlorothiazide had been prescribed for her mother for hypertension. Findings on physical examination were unremarkable except for mild orthostatic hypotension.

Laboratory studies disclosed the following values: serum sodium 115 (normal, 135 to 145), serum potassium 3.4 (3.5 to 5), serum chloride 73 (96 to 106) and serum bicarbonate 20 mEq per liter (24 to 32); BUN 90 (8 to 24), creatinine 2.2 (0.6 to 1.4) and calcium 10.5 mg per dl (8.5 to 10.5); albumin 5.1 grams per dl (3.5 to 5), and uric acid 11.1 (3.5 to 8) and glucose 106 mg per dl. Results of liver function tests were within normal limits. Another chemistry panel gave the following findings: sodium 122 and potassium 2.9 mEq per liter, BUN 57, creatinine 1.7 and calcium 10.6 mg per dl.

Hypoadrenalism was considered, but ruled out by normal results on a one-hour cosyntropin stimulation test, with a peak cortisol level of 45 μg per dl. The hypercalcemia was thought to be due to dehydration, which was confirmed by repeatedly normal ionized calcium determinations. The serum parathyroid hormone concentration (Upjohn Laboratories, Kalamazoo, Michigan) was appropriate for the level of ionized calcium. Urinary calcium was 46 mg per gram of creatinine (normal, 50 to 250). Spot urine sodium was 1 mEq per liter and urine potassium was 10 mEq per liter. A serum aldosterone determination was done on a specimen taken while the patient was in a supine position and gave a value of greater than 300 ng per dl (normal, 2 to 9); plasma renin activity was reported 22.8 ng per ml an hour (normal, 1.1 to 7.9).

The electrolyte acid-base findings suggested a gastrointestinal-caused electrolyte loss. However, given the history of polyuria, xerostomia, hypercalcemia and pancreatitis, and the known maternal consumption of diuretics, we screened a urine specimen for thiazides. A urinary thiazide concentration of 7 μg per ml was found. Urine electrolyte studies done at the same time showed a sodium concentration of 2 mEq per liter and potassium of 27 mEq per liter; chloride was not measured. The low urinary sodium level in the presence of diuretic use suggested that gastrointestinal electrolyte loss was mainly responsible for her serum electrolyte abnormalities.

She subsequently admitted to having moderate diarrhea but she would not elaborate as to quantity or type of stool excreted (watery versus formed, and so forth). After confrontation, she continued to deny diuretic and laxative use. The patient was referred back to her primary physician with diagnoses of (1) hypercalcemia, xerostomia and pancreatitis due to thiazide abuse and (2) electrolyte abnormalities due to a combination of gastrointestinal and thiazide-induced losses.

CASE 2. A 30-year-old woman was referred to our endocrine clinic for evaluation of hypokalemia. She noted a purposeful weight loss from ages 12 to 20, and a psychiatric admission during adolescence. She gave a history of cyclic edema in her early 20's.

Six years previously she had been admitted to a university hospital for investigation of explosive diarrhea and hypokalemia. No cause was found. In March 1981 a routine electrolyte screening was done before a dental surgical procedure. Initial evaluation showed hypokalemia, thought to be due to Bartter's syndrome,[1] and she was referred to our clinic. She had moderate muscle weakness and said she had not eaten any licorice, laxatives or diuretics. Findings on physical examination were unremarkable and there was no evidence of postural blood pressure variation or edema.

Laboratory results included sodium 139, potassium 2.8, chloride 86 and bicarbonate 36.3 mEq per liter; BUN 17 mg per dl; a supine plasma renin activity determination measured 12.7 ng per ml per hour and serum aldosterone 20 ng per dl. Spot urine analysis showed a sodium value of 176 and a potassium level of 61 mEq per liter. The urine electrolyte loss suggested the possibility of diuretic use, which was confirmed by the finding of urinary furosemide concentration of 7 μg per ml. Tests of urine were negative for thiazide concentrations.

She was confronted but would not admit to furosemide abuse. She asked that we repeat the urine tests. Repeat screening of the urine showed it to be negative for furosemide, but positive for thiazide (22 μg per ml). She continued to deny intermittent use of different diuretics and she was referred back to her primary physician for further therapy.

Methods

Electrolytc determinations were done on an autoanalyzcr (Technicon). Analysis of plasma renin activity was done by University of California laboratories.[2] Serum aldosterone radioimmunoassays were carried out at Nichols Institute, San Pedro, California.[3] Both urine furosemide and urine thiazide quantities were determined by Hines Laboratory, San Francisco. Urine furosemide concentrations were measured using a fluorometric assay.[4] Values less than 2 μg per ml may be related to nonspecific urinary fluorescent activity. Values greater than 2 μg per ml are specific. Urine thiazide determinations were done colorimetrically.[5] The assay is specific for thiazides but cannot differentiate chlorothiazide from hydrochlorothiazide.

Discussion

The known ingestion of furosemide and thiazide diuretics is associated with multiple and easily recognizable side effects.[6,7] When diuretic use is covert, however, the consequences may be ascribed to myriad other causes.

Diuretic abuse is most common in women who may be health professionals and tend to be preoccupied with either weight loss or edema.[8-10] They may go to incredible lengths to conceal their medication habit. Patients have undergone selective venous catheterization,[11] placement of a shunt permitting venous access for prolonged potassium administration[11] and renal biopsy[12,13] before admitting to taking a diuretic.

Electrolyte abnormalities are the most common side effects of diuretic use[6] and abuse.[11-21] Hyponatremia, as seen in case 1, occurs when impaired free water clearance caused by diuretics is accompanied by increased water ingestion.[22] Hypokalemia and hypochloremic alkalosis can be consequences of both thiazide and furosemide use.[23,24] The hypochloremic acidosis of case 1 suggests that thiazides alone could not have induced the electrolyte acid-base abnormality. The low serum bicarbonate level is probably due to diarrhea, and the hypochloremia to ingestion of diuretics. A mixed gastrointestinal-diuretic cause is further supported by the low urine sodium and positive result of urine thiazide assay.

Both furosemide and thiazides can produce volume depletion. The patient in case 1 had sufficient volume contraction to cause mild postural hypotension, xerostomia and an elevated BUN level. Given her denial of gastrointestinal symptoms or diuretic use, studies had been done for Sjögren's syndrome and renal disease.

Volume deplction results in increased renin production by the juxtaglomerular apparatus, with secondary rise in aldosterone levels.[25] Both furosemide and thiazides can induce hypokalemia by direct renal tubular effects.[23] The hyperaldosteronism due to volume depletion further contributes to renal potassium wasting. The consequent hypokalemia can present as muscle weakness or may be interpreted as arthralgias (case 1). The combination of hypokalemic-hypochloremic alkalosis and increased serum renin and aldosterone concentrations that is seen in association with diuretic abuse can mimic Bartter's syndrome.[12-16,26,27]

In 1962 Bartter and co-workers[1] described a syndrome of short stature, hypokalemia, increased renin and aldosterone levels, and normal blood pressure. Juxtaglomerular apparatus hyperplasia was found on cxamination of a renal biopsy specimen and there was a decreased hypertensive response to angiotensin infusion. Recent studies have helped clarify the pathophysiology of Bartter's syndrome. Although not firmly established, the primary defect would appear to be decreased chloride reabsorption in the ascending limb of thc loop of Henle.[28] This results in increased urinary chloride and potassium excretion and in hypokalemia. The increased renal prostaglandin production that occurs in Bartter's syndrome[29] may be due to hypokalemia,[30] but other stimuli such as angiotensin II, bradykinin, vasopressin and polyuria have been suggested.[31] Prostaglandins increase renin production by the juxtaglomerular cells. Constant juxtaglomerular apparatus stimulation results in juxtaglomerular cell hyperplasia. Renin via angiotensin II augments adrenal production of aldostcrone. Prostaglandins may also increase synthesis of bradykinin, which, in conjunction with volume depletion, prevents hypertension in the face of endogenous or exogenous angiotensin II.[32,33]

The primary action of furosemide is to inhibit chloride reabsorption in the ascending limb of Henle's loop.[34] Thiazides also promote urinary excretion of chloride.[35] If the chloride reabsorption defect proposed for Bartter's syndrome is correct, it follows that furosemide and thiazides could induce a state very analogous to Bartter's syndrome (pseudo-Bartter's syndrome, type I). In fact, examination of renal biopsy specimens in two

cases of covert furosemide use have confirmed juxtaglomerular cell hyperplasia.[12,13] The only way to differentiate true Bartter's syndrome from diuretic induced pseudo-Bartter's syndrome, type I, would seem to be by repeatedly screening for furosemide and thiazides.

Prolonged laxative abuse[18,36,37] or emesis,[38,39] or both, can also produce a pseudo-Bartter's syndrome, accompanied by juxtaglomerular apparatus hyperplasia.[36,37,39] In contrast with true Bartter's syndrome or the diuretic-induced states, gastrointestinal electrolyte loss is accompanied by low urine chloride levels[38] (pseudo-Bartter's, type II). Combined diuretic and laxative abuse with variable urinary electrolyte measurements has been described.[18]

Pseudo-Bartter's syndrome may account for many of the cases presenting in adulthood. The true syndrome is usually diagnosed in children[40] but has been reported in adults as old as age 74.[41] Some of the adult patients have had symptoms dating to early childhood, and in others surreptitious vomiting or laxative or diuretic abuse had not been eliminated. Therefore, true adult Bartter's syndrome would seem to be a very rare occurrence. Repeated determinations of urinary chloride and diuretic concentrations should be done before embarking on costly and invasive investigations for the adult syndrome.

Thiazides inhibit urine calcium excretion[42] and can raise both serum total[42] and ionized[43] calcium levels. An association between thiazide use and hyperparathyroidism has been suggested.[44] The hypercalcemia in case 1 was probably due to volume depletion, as indicated by the high serum albumin and normal ionized calcium levels. Nevertheless, the persistently mild hypercalcemia had prompted investigations for sarcoidosis and hyperparathyroidism.

Thiazide use probably contributed to the repeated bouts of pancreatitis seen in case 1. An association of thiazides and pancreatitis is described.[45,46] Cholelithiasis, which was not present in our patient, may also be thiazide-related.[47]

Other side effects of thiazide or furosemide use might occur with covert ingestion (Table 1). These include cardiac arrhythmias,[24] thrombocytopenia,[48] skin rash,[49,50] hypomagnesemia with or without hypocalcemia,[51] auditory abnormalities,[52] hyperuricemia,[53] carbohydrate intolerance,[54] interstitial nephritis[55] and cyclic edema.[8]

The patient in case 2 had a history of edema.

TABLE 1.—*Clinical Abnormalities That Suggest Covert Diuretic Use*

Taking Diuretics Only
Electrolyte abnormalities
Hyponatremia
Hypokalemia
Hypochloremic alkalosis
Hypercalcemia, hypomagnesemia, hypocalcemia
Other abnormalities
Polyuria, nocturia
Volume depletion, xerostomia
Pancreatitis
Skin rash
Thrombocytopenia
Hearing loss
Cardiac arrhythmias
Elevated blood urea nitrogen and/or interstitial nephritis
Hyperuricemia
Hyperglycemia
Taking Diuretics Plus Laxatives
Hypokalemic acidosis
All of the above listed abnormalities

MacGregor and colleagues[8,56] have studied patients with idiopathic edema. All were taking diuretics. Several patients had the onset of swelling only after beginning diuretic use. Most had worsening of edema after they stopped taking these drugs, with resolution within two to three weeks. High renin and aldosterone concentrations were found in these patients for up to four weeks after diuretic intake was stopped. Thus, many cases of idiopathic edema may be due to overt or covert diuretic ingestion.

Summary

Covert diuretic abuse can present in a variety of diagnostic disguises. The general availability of assays for thiazides and furosemide can help prevent expensive and potentially dangerous investigations. Use of these assays is suggested for patients with electrolyte acid-base disturbances of obscure origin. Diuretic screening also seems indicated when prototype patients (that is, a woman, a health worker and so forth) have disorders of unknown cause accompanied by electrolyte abnormalities and the clinical features can be associated with known diuretic toxicity.

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Refer to: Nishimura RN, Koller R: Isolated cortical blindness in pregnancy. West J Med 1982 Oct; 137:335-337

Isolated Cortical Blindness in Pregnancy

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ISOLATED CORTICAL BLINDNESS due to preeclampsia or eclampsia is unusual. Recently we saw two patients with this syndrome. Reports of their cases

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No reprints are available.

and a brief discussion of localization of the problem in the occipital cortex are presented.

Reports of Cases

CASE 1. The patient, a 16-year-old girl who was 36 weeks pregnant, had an abruptly occurring visual loss. At 35 weeks of pregnancy, she was noted to have peripheral edema and proteinuria (a trace), but a blood pressure in the normal range. Two days before her admission, moderate headaches developed and she had visual blurring, nausea and vomiting. Her vision deteriorated so that she could distinguish only light and dark. Her blood pressure was 140/90 mm of mercury. There was mild pedal edema. A neurologic examination showed her neck to be supple. A mental status examination found no abnormalities. Pupils were round and briskly reactive to light. A fundoscopic examination showed sharp discs with venous pulsations. There was no optokinetic nystagmus. Visual acuity was reduced to light appreciation only and wandering eye movements were noted. On the remainder of the neurologic examination, including sensory examination, no abnormalities were noted.

Laboratory tests gave normal results on a complete blood count and serum chemistry determinations. Findings on a lumbar puncture, a computerized tomography brain scan and skull x-ray studies were normal. Analysis of urine showed a reaction for protein of 2+.

The patient initially received magnesium sulfate and hydralazine hydrochloride given intravenously to control hypertension. After an induced delivery, the patient's vision gradually improved and within three days her visual acuity was 20/20 with mildly abnormal color plate perception. An electroencephalogram done at this time showed prominent polymorphic 4 to 7 Hz activity in the occipital regions. A week after the delivery, the patient's vision and blood pressure were normal.

CASE 2. The patient, 35 years old and 37 weeks pregnant, was admitted to hospital following a grand mal seizure. She received routine prenatal care and had done well until 72 hours before admission when a moderate generalized headache developed and she was noted to be moderately hypertensive. Examination at the time of admission showed her blood pressure to be 160/110 mm of mercury. Findings on general examination were normal and she had no peripheral edema. Neurologic examination showed her to be confused, disoriented and unable to see. Pupils were 3 mm, equal and briskly reactive to light. There was no optokinetic nystagmus. Visual acuity was reduced to light perception only. Muscle stretch reflexes were brisk and symmetric and the rest of the examination showed no abnormalities. On ophthalmologic consultation the fundoscopic examination gave normal findings. Laboratory studies gave normal values for serum chemistries and normal complete blood count, platelet count, fibrinogen and coagulation. Proteinuria was noted (a trace). Findings on a computerized tomographic scan were normal. An electroencephalogram showed slowing of the dominant frequency with diffuse polymorphic theta activity.

The patient initially received magnesium sulfate and hydralazine (given intravenously) to control hypertension. Following a cesarean section her condition rapidly improved and within three days findings on neurologic and ophthalmologic examinations were normal.

Discussion

About 30 percent to 50 percent of eclamptic women have visual symptoms, often associated with retinal arteriolar spasm, hemorrhages and exudates.[1,2] Neither of our patients had retinal abnormalities to explain their visual loss. Blindness associated with normal fundi and pupillary function suggests retrogeniculate visual dysfunction. Blindness caused by a prechiasmal lesion either in the retina or optic nerve would be expected to disturb pupillary function. A chiasmal lesion of the optic pathways is associated with bitemporal visual field abnormalities and when caused by pituitary adenomas during pregnancy may resolve completely after delivery.[3,4] An insult to the optic radiations or primary visual cortex would be expected to spare pupillary reaction to light because fibers controlling this have left the primary optic pathways in the midbrain. Lesions of the optic radiations or tract spare optokinetic nystagmus, a cortical function. In lesions affecting the primary visual cortex the optokinetic nystagmus response is absent. We believe that our patients had cortical blindness, a diagnosis supported by electroencephalography in case 1 that showed theta activity in the occipital region and in case 2 generalized slowing.

It is tempting to postulate that vasospasm of the posterior cerebral arteries or their distal branches leads to relative ischemia and was re-

sponsible for the loss of vision. Vasospasm is also associated with migraine, though it is less likely as a cause because both patients' visual loss resolved coincidentally with delivery and neither had a history of vascular headaches. Thrombosis or emboli in the distribution of the posterior cerebral arteries are unlikely without permanent deficits.

Other cases of cerebral blindness have been reported to occur during pregnancy and are described in eclampsia,[1] hypertensive encephalopathy[5] and postpartum sinus thrombosis.[6,7] Data derived from pathology studies suggest that microinfarctions and hemorrhages are the basis of these disease states.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Photon Absorptionmetric Procedure

QUESTION:

Is the photon absorptionmetric procedure, using the Norland-Cameron Bone Mineral Analyzer, an acceptable diagnostic test for osteodystrophy, osteomalacia, osteopenia, senile osteoporosis, Paget's disease? If acceptable, what is the frequency with which this test should be performed?

OPINION:

It is the opinion of the Advisory Panels on Nuclear Medicine, Radiology, Orthopedics, Internal Medicine and Pathology that the photon absorptionmetric procedure, using the Norland-Cameron Bone Mineral Analyzer, is an acceptable test for diagnosing and following therapy of patients with osteodystrophy, osteomalacia, osteopenia, senile osteoporosis and Paget's disease. The frequency of the procedure is generally in the range of three to nine months, depending upon the clinical problem being addressed. In postmenopausal women, the frequency is generally once every one to two years.

Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Patients With Cervical Cancer

To the Editor: The article by Chu and coworkers[1] in the July issue reports on quality of care in women with stage I cervical cancer (invasive and noninvasive). The authors report but do not comment upon the lack of difference in outcome whether the patients received their preconceived optimum or less than optimum care. Their study would be greatly enhanced by knowing what forms of so-called nonoptimum care resulted in no increase in death rate or recurrence of the disease. Perhaps unknowingly they may have discovered a more cost effective method of treating patients with cervical cancer.

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REFERENCE

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* * *

Drs. Chu and Tamimi Respond

To the Editor: In response to Dr. Kornfield's letter, we would like to comment on three points.

First, the lack of difference in the survival between optimal and suboptimal care groups was addressed in the "Comment" section of the paper:

> The lack of difference in the three-year survival rates between the optimal and suboptimal care groups in stage IA cervical cancer is not surprising because most of the patients classified as suboptimal underwent simple hysterectomy for suspected carcinoma in situ and were diagnosed as having microinvasive cervical cancer from the pathologic specimen. So, even though patients did not have an optimal diagnosis, they did finally receive the standard definitive treatment. There was also no significant difference in survival rates between the optimal and suboptimal groups in stage IB. This lack of difference was probably due either to the short follow-up time or the possible efficacy of radiation immediately after simple hysterectomy, or both.[10,11]
>
> It should be noted that 22 women with stage IB cervical cancer in the suboptimal group received simple hysterectomy followed by radiation.

Second, although we did classify the women into optimal and suboptimal care groups, the criteria used for classification were not "ours." The criteria used were those recognized to be the "standard of care" by most experts in the field.

Third, our study is not designed to evaluate efficacy of different types of therapies for stage I cervical cancer, but rather to explore the different characteristics of patients, hospitals and doctors. Selection bias as well as other problems precludes the comparison of the survival rates to measure efficacy of treatment.

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Radiology and Medical Care Costs

To the Editor: This is in regard to the August 1982 article "The Costs and Risks of Medical Care."[1] As a practicing general radiologist, I have seen tremendous changes in diagnostic imaging over the past five years. I have a full-time job keeping up with the changes. There is now a tremendous overlap of diagnostic imaging available for certain disease states; for example, surgical versus medical jaundice, evaluation of pancreatic size, and the use of hypertensive pyelograms. Physicians order tests in a manner that was present in the medical training of 1960. That is, the attending physician orders hypertensive intravenous pyelograms, oral cholecystography or other studies. I am sure that if there was consultation between practicing physicians and the radiologists before the tests were ordered, the number of tests would decrease and the yield of information would increase. It has been suggested that a consulting radiologist in a department to plan the type of tests for diagnostic problems would decrease the costs of medical care. The high cost of imaging and the significant difference in yield

were pointed out in the lead article, concerning acute cholecystitis, in the August issue.[2]

Another problem is general practitioners with their own x-ray equipment. There is no doubt that this is a great money-maker and the cost of excess x-ray testing probably reaches millions of dollars in California alone. This is to say nothing about the lack of radiation control and film quality.

I think these two problems, when corrected, would decrease patients' costs.

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Waterborne Transmission of *Campylobacter*

Campylobacter organisms are a common cause of diarrheal illness, found in approximately 5 percent of stool specimens cultured for bacterial pathogens by the Washington State Public Health Laboratory. *Campylobacter* sp have been isolated from seawater[1] and waterborne transmission has been reported in three outbreaks.[2-4]

As a result of bacterial surveys of water supplies in Washington state, we have isolated *Campylobacter* organisms from three sources of raw surface water (lakes). In each case neither total nor fecal coliforms were significantly elevated in the samples and no source of contamination was identified. It is possible that infected waterfowl or other wildlife were responsible for the contamination.

Although *Campylobacter* infections usually cause symptoms distinctly different from those associated with giardiasis, the symptoms can be nearly indistinguishable. Since both infections may result from consumption of untreated surface water, both are possible causes of diarrheal illness among persons with a recent history of untreated water consumption. Exhibiting a shorter incubation period than giardiasis, *Campylobacter* infection should be considered in patients with diarrhea when untreated water has been consumed within seven days of the beginning of symptoms.

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The Pot and the Kettle

To the Editor: Talk about the pot calling the kettle black!

MSMW must be steamed up about *encounter;* so much so, he doesn't see (in his August editorial)[1] the same evil in saying *lexicon* when he means *vocabulary*; isn't bothered a whit about preferring *professional happening* (happening!!) to *encounter*; and seems smug when he senses steps, especially steps that degrade semantically, and best of all, steps that degrade relationships.

Justifiably riled about *providers* and *consumers,* he uses the same claptrap when he has them *interacting professionally* (implying, I guess, that patients are professional), not to mention interacting in delivery. Narrowly escaping *hopefully,* he's so careful to say "it is to be hoped" that he forgets to stick a comma on both sides of a plainly independent clause.

He's so upset by *encounter* that he doesn't vomit when he says "meaningful doctor-patient relationship" (that's to distinguish it, I suppose, from meaning*less* relationships). Because of his distress, we can overlook *usage* when *use* would do nicely, but it's unforgivable to somehow justify the jargon he not only criticizes but uses, by saying that "language is made up of the words people use and the ways they use them." Stopping there ignores the corollaries that language can be simple, effective, direct, clear and beautiful, or it can be, as in his case, dull, trite, puffed-up, muddy and ugly. If I were Malcolm S. M. Watts, MD, and if I were editor of The Western Journal of Medicine, and if I wrote like that, I'd sign it MSMW, too, out of embarrassment—irrespective of whether I ever used the world *(sic).*

JAMES B. SMITH, MD
Seattle

REFERENCE

1. On having encounters with patients (Editorial). West J Med 1982 Aug; 137:129

Editor's Note: Touché × 3(?)—Whoopee!!
—MSMW

Refer to: White RH: Shoulder pain (Topics in Primary Care Medicine). West J Med 1982 Oct; 137:340-345

Shoulder Pain

RICHARD H. WHITE, MD, *Sacramento, California*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

PRIMARY CARE PHYSICIANS frequently see patients who have pain and loss of normal motion in the shoulder. It is gratifying for a clinician to evaluate this condition because, in most cases, a carefully elicited history and a physical examination are all that are necessary to arrive at a diagnosis. This discussion will review the important functional anatomy of the shoulder, outline an approach to the care of a patient who has symptoms confined to the shoulder and describe the clinical features of the most common syndromes. Several excellent reviews of shoulder pain have been published recently for those who desire a more detailed discussion (see "General References").

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The complex motion of the shoulder is the result of movements of four joints: the glenohumeral, the acromioclavicular (AC), the sternoclavicular and the scapulothoracic. Coordinated movement of each of these joints occurs during complex shoulder maneuvers like throwing, so that derangements affecting any of these joints may result in abnormal shoulder motion. Restricted motion of one joint usually causes an alteration in the normal motion of the other shoulder joints.

A variety of disorders, including cervical spine disease, neurologic dysfunction, thoracic outlet syndrome(s), systemic arthritis and neoplasm, may produce pain in the vicinity of the shoulder either by direct involvement or via referred pain mechanisms. The most common causes of shoul-

der pain and their important clinical features are listed in Table 1.

Anatomy of the Shoulder Joint

Pain that is felt "in" the shoulder joint is usually due to processes affecting the glenohumeral joint, the AC joint or the soft tissues of the shoulder, which include the joint capsule, supporting ligaments, the rotator cuff and the long head of the biceps tendon. Important anatomic relationships are depicted in Figure 1. Note that the long head of the biceps tendon, which originates on the superior rim of the glenoid, passes down the anterior aspect of the humerus in a groove between the greater and lesser tuberosities. The acromion and the coracoacromial ligaments provide a roof over the humeral head and the rotator cuff tendons.

The points of insertion of the rotator cuff tendons and the location of the subacromial bursa are shown in Figure 2. This bursa, which occasionally is referred to as the subdeltoid or supraspinatus bursa, lies directly under the acromion and the deltoid muscle immediately above the tendons of the rotator cuff and the humeral head. When inflammation develops in the tendons, the overlying bursa frequently becomes inflamed also.

History and Examination

Important information to elicit from a patient having shoulder pain includes a history of recent or remote shoulder trauma or excessive occupational stress, the presence of associated symptoms suggesting a systemic or neurologic disorder, the exact location and duration of the pain and factors that increase or diminish the pain. Pain in the region of the AC joint suggests a local problem, whereas pain over the anterior or lateral aspect of the humerus suggests a biceps tendon or rotator cuff problem. Pain extending from the acromion to the lower part of the deltoid generally reflects deep inflammation in the rotator cuff tendons.

TABLE 1.—*Differential Diagnosis of Shoulder Pain With Distinguishing Clinical Characteristics*

Diagnoses	*Clinical Features*
Rotator cuff lesions	
Degenerative tendinitis or bursitis	Dull pain worse at night; painful arc between 60° and 120° abduction
Calcific tendinitis or bursitis	Men and women equally affected; begins abruptly; pronounced tenderness; calcium deposits seen on x-ray films
Rotator cuff tears, partial or complete	Older than 50 years; history of trauma; weak abduction and muscle spasm with complete tears; passive range of motion normal
Biceps tendon lesions	
Tendinitis, tenosynovitis	Anterior shoulder pain; tender bicipital tendon; painful resisted supination of the forearm with elbow at 90°
Elongation or rupture	Weakness; long belly lax when biceps contracted; lump appears after rupture
Dislocation	Painful external rotation with snap, relieved by medial rotation
Adhesive capsulitis or "frozen shoulder" Primary (idiopathic) Due to immobilization following injury, tendinitis, bursitis	Diffuse pain and tenderness, reduced active and passive motion; no improvement in motion after injecting local anesthetic; arthrogram shows contracted capsule
Reflex sympathetic dystrophy	Similar to adhesive capsulitis along with pain, swelling, tenderness and skin changes in the hand; vasomotor instability
Osteoarthritis	
Acromioclavicular joint	Painful abduction 140° to 180°; shrugging motion painful; local tenderness
Glenohumeral joint	Following trauma or associated with calcium pyrophosphate deposition; mild pain; restricted motion
Trauma, including nerve injuries	History, findings on physical examination and radiographs make diagnosis
Septic arthritis	Joint effusion; painful motion; fever; elevated leukocyte count
Systemic diseases including the arthritides and metabolic-endocrine disorders	Signs and symptoms of systemic process
Other musculoskeletal disorders such as fibromyalgia and polymyalgia rheumatica (PMR)	Pain and stiffness more generalized and symmetric; painful trigger points with fibromyalgia; age older than 50 years with high sedimentation rate in PMR

When inflammation persists for many months the pain may radiate down the arm as far as the wrist, in the distribution of the C5 dermatome.

A complete physical examination should include careful examination of the cervical spine, a detailed neurologic examination and a thorough examination of the affected extremity. The shoulder should first be carefully inspected for atrophy, fasciculations, swelling or erythema. Palpation of the AC joint may elicit moderate tenderness following an injury or when advanced degenerative arthritis is present. A glenohumeral joint effusion is best felt just lateral to the coracoid process, which should be easily identified anteriorly. With the arm in external rotation (palms forward) the anterior aspect of the humerus should be gently palpated with the thumb. The long head of the biceps tendon can usually be felt in the intertubercular groove just medial to the prominent anterior aspect of the greater tuberosity. Whereas palpation may elicit moderate tenderness in many normal persons, exquisite tenderness is noted in patients with bicipital tendinitis. The greater tuberosity should be examined next. Maximal tenderness in this region suggests supraspinatus tendinitis, bursitis or a supraspinatus tendon tear. Tenderness over the posterior aspect of the greater tuberosity suggests inflammation in the infraspinatus or teres minor tendon.

Next, range of shoulder motion must be observed and carefully noted. In most cases assessment of active range of motion using five maneuvers will yield the essential information. First, ask a patient to lift both arms away from the body and reach as high above the head as possible (abduction, see Figure 3). Second, have the patient raise both arms directly forward until they touch overhead (flexion). Third, have the patient place one hand and then the other behind the back and touch as high on the back as possible (internal rotation). Fourth, with the elbows flexed

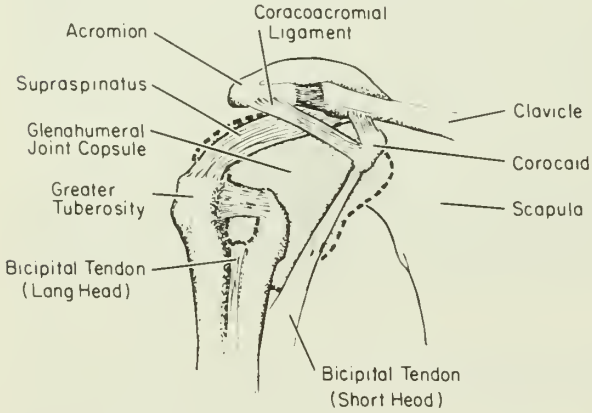

Figure 1.—Anterior view of the shoulder showing the joint capsule and important surrounding structures.

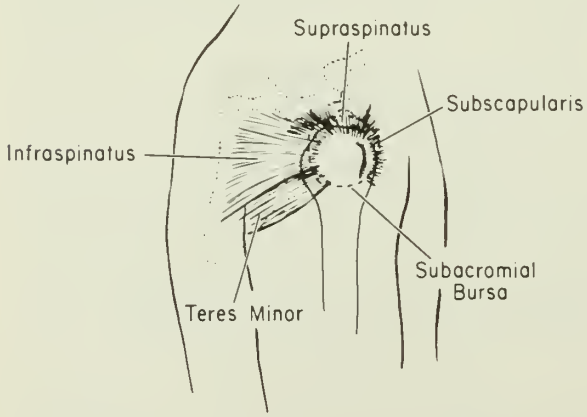

Figure 2.—Lateral view of the shoulders showing the points of insertion of the rotator cuff and the location of the subacromial bursa.

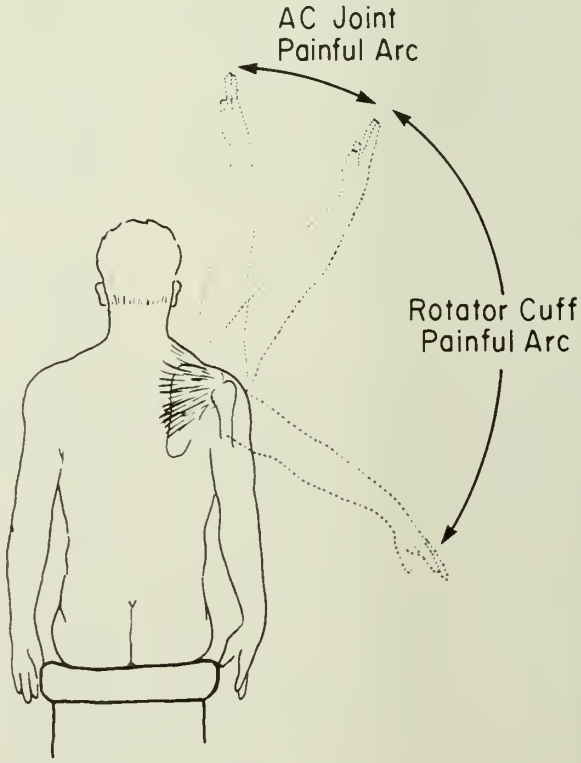

Figure 3.—Abduction of the shoulder. Pain arising from rotator cuff tendinitis or bursitis causes pain between 60 degrees and 100 to 120 degrees whereas AC joint inflammation causes pain between 140 degrees and 180 degrees. Pain due to rotator cuff tendinitis may disappear when the arm is abducted above 100 degrees to 120 degrees.

at 90 degrees and held against the body, have the patient turn the arms out (external rotation). Fifth, ask the patient to actively shrug and protrude the shoulders to test the sternoclavicular and the AC joints. Motion against resistance during each of these maneuvers may be extremely useful in eliciting pain and thereby identifying inflamed tissues, especially when shoulder pain is mild. Finally, after measuring active range of motion, a physician should test passive range of motion, particularly abduction, flexion and external rotation.

Although one can frequently diagnose the cause of shoulder pain clinically, plain radiographs are useful in showing calcific deposits in the rotator cuff tendons, calcium pyrophosphate deposition in the articular cartilage and primary or secondary degenerative changes in the humeral head, the AC joint and the glenohumeral joint. Arthrography is very helpful in diagnosing complete rotator cuff tears and adhesive capsulitis.

Major Clinical Syndromes

Rotator Cuff Tendinitis and Bursitis

Inflammation occurs frequently in the tendons of the rotator cuff, particularly in the supraspinatus tendon, as a result of repeated occupational or recreational trauma to the shoulder. Bursitis arises due to inflammation of the rotator cuff tendons. Patients are usually middle-aged and have a dull ache in the region of the deltoid, worsened by sleeping on that side or raising their arm in abduction. With the arm at the side in external rotation, tenderness may be elicited anteriorly (subscapularis or biceps), over the greater tuberosity (supraspinatus) or more posteriorly (infraspinatus). Active abduction usually brings on severe pain between 60 degrees and 100 to 120 degrees of abduction—called "the painful arc"—when the inflamed rotator cuff and the overlying bursa are forced under the acromion and coracoacromial ligament. Patients are usually unable to abduct the arm beyond 60 degrees without initiating scapular motion with a shrug to lift the arm higher. If the arm can be abducted beyond 100 degrees to 120 degrees the intensity of the pain may decrease considerably. Passive range of motion is usually close to normal but may be restricted because of pain. Infiltration of the region of the rotator cuff with 2 ml of 1 percent lidocaine solution usually relieves the pain and allows full range of motion. In most cases findings on radiographs are normal, but secondary degenerative changes may be seen in the greater tuberosity, the AC joint and the undersurface of the acromion, particularly in patients with chronic shoulder pain.

Treatment to help relieve pain usually consists of support of the shoulder in a sling for several days, use of nonsteroidal antiinflammatory agents such as aspirin or indomethacin and physical therapies such as ultrasound and local application of heat or cold packs. A simple physical therapy program should be initiated as soon as possible with the aim of preserving full range of motion and preventing adhesive capsulitis or a reflex sympathetic dystrophy. Full immobilization of the shoulder should be avoided. If a physical therapist is not available, family members should be taught how to assist the patient in gentle passive range of motion exercises, which should be done several times each day. Pendulum exercises are the next step, in which a patient is instructed to lean forward and slowly swing the dangling arm back and forth, first in the plane across the front of the body and then along the side for ten minutes three times a day, gradually increasing the amplitude of each swing as tolerated. The use of a light 3- to 5-lb (1.4 to 2.3 kg) weight in the hand may help to stretch the tissues in the shoulder. If pain and restricted motion persist, injection of a mixture of 1 ml of 1 percent lidocaine and 20 to 40 mg of methylprednisolone acetate (the crystalline form of the steroid) or its equivalent into the bursa adjacent to the involved tendon may provide long-term relief. Preventive measures include reduction of recreational or work-related shoulder stress and, in selected cases, surgical intervention to relieve chronic rotator cuff impingement.

Calcific Tendinitis and Bursitis

Radiographically evident calcium deposition (hydroxyapatite) develops in the tendons of the rotator cuff in as many as 8 percent of persons over 30 years of age. The pathogenesis of the calcium deposition is unknown but the process is frequently bilateral and usually asymptomatic. In patients with clinical evidence of rotator cuff tendinitis, the radiographic finding of tendon calcification may be a marker for a degenerative process occurring in these tendons. In some persons, however, the calcium deposits may enlarge and spontaneously rupture into the overlying subacromial bursa, producing an acute, extremely painful, crystal-induced bursitis. The clinical

presentation is dramatic. Marked spasm develops in the shoulder muscles and a patient will hold the elbow tightly against the side to splint any motion. Gentle palpation of the shoulder elicits exquisite tenderness and findings on x-ray films show an oval deposit of calcium between the humeral head and the acromion.

Treatment of an acutely inflamed shoulder includes sling support, liberal use of analgesic medications and prompt injection of 2 ml of 1 percent lidocaine mixed with 40 mg of methylprednisolone acetate or its equivalent into the tendon sheath adjacent to the calcific deposit, followed by a program of gradual shoulder mobilization. If symptoms do not subside in several weeks, the region should be reinjected with an anesthetic and steroid mixture and, after anesthesia has been attained, the calcific mass should be probed with a needle several times in an attempt to free calcium crystals. The long-term prognosis is very good.

Rotator Cuff Tears

Complete rotator cuff tears rarely occur in young persons, but this condition is commonly seen in persons older than 50 years. Classically, in a patient who has had a long history of excessive shoulder use, pain suddenly develops during lifting or after falling. Shoulder pain intensifies about 12 hours later and a patient is unable to abduct the affected arm. On examination severe muscle spasm and normal *passive* range of motion to at least 90 degrees of abduction will be seen. An important sign is frankly weak abduction, as evidenced by the inability to hold the arm at 90 degrees without support or collapse of the abducted arm when minimal downward pressure is applied by the examiner (drop arm sign). Downward traction on the arm or dangling the arm like a pendulum may help to relieve the pain. Arthrography may establish the diagnosis by showing direct continuity between the glenohumeral joint and the subacromial bursa. Arthrography should be done immediately in any patient suspected of sustaining a complete rotator cuff tear who is an appropriate candidate for surgical treatment and, if a tear is present, the patient should be referred to an orthopedic surgeon. Partial tears are difficult to diagnose clinically because signs and symptoms of partial tears mimic rotator cuff tendinitis. Partial tears may be managed conservatively.

Bicipital Syndromes

Inflammation confined to the tendon of the long head of the biceps generally occurs in persons who stress this tendon by repetitive motion of the arm using a pulling or throwing motion. Extreme tenderness is noted when the tendon is palpated in the bicipital groove. With the arm externally rotated and extended at the elbow, flexion of the shoulder against resistance produces pain. Forced supination of the forearm with the elbow flexed at 90 degrees also causes pain in the long head of the biceps tendon. Some patients feel a painful "snap" when they externally rotate and abduct the shoulder, and palpation may find the tendon slipping out of the bicipital groove. A painful arc during flexion or abduction suggests that rotator cuff inflammation is also present.

Treatment of bicipital tendinitis includes discontinuation or alteration of the repetitive shoulder motion responsible for the irritation, use of nonsteroidal antiinflammatory agents and, on occasion, local injection of 20 mg of methylprednisolone acetate or its equivalent into the tendon sheath. Repeated injections of corticosteroid may weaken the tendon and lead to eventual rupture. Surgical therapy is indicated for a dislocating tendon and chronic bicipital tendinitis unresponsive to medical therapy.

Adhesive Capsulitis

The terms adhesive capsulitis and "frozen shoulder" refer to a disorder characterized by the gradual onset of diffuse shoulder tenderness together with greatly reduced active *and* passive range of motion that does not improve following the instillation of a local anesthetic adjacent to the rotator cuff. The pathogenesis is unknown, but it usually develops after prolonged immobilization of the shoulder and has been reported in patients with shoulder trauma, rotator cuff tendinitis, cervical spine disease and rheumatoid arthritis. The normally voluminous joint capsule becomes contracted and fibrotic. There is speculation that this condition may be a limited form of a reflex sympathetic dystrophy.

On physical examination there is diffuse shoulder tenderness and reduced range of motion in all planes. Radiographs frequently show osteopenia of the humeral head. Arthrography may be diagnostic because in essentially all cases there is a frankly contracted joint capsule with loss of

bursal outpouchings. The disorder may last for several years and be characterized by an initial period of increasing pain and stiffness followed by a period of restricted motion with diminished pain followed by a gradual return of motion with abatement of pain.

The best treatment is prevention with early rehabilitation of any painful or immobilized shoulder using range of motion exercises and physical therapy. Although no controlled studies have been reported, a variety of therapies have been advocated including intensive physical therapy, oral administration of corticosteroids in the early phases and injection of approximately 50 ml of saline mixed with a local anesthetic and the equivalent of 40 mg of methylprednisolone acetate into the joint under pressure, a procedure called infiltration brisement.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy, also known as Sudeck's atrophy or the shoulder-hand syndome, is a poorly understood disorder that is frequently associated with pain and restricted motion in the ipsilateral shoulder. Certain unique clinical features easily differentiate reflex sympathetic dystrophy from other causes of shoulder pain. In addition to shoulder pain that mimics adhesive capsulitis, a patient will have moderate to severe burning pain, swelling and pronounced tenderness of the fingers and hand and signs of vasomotor instability in the arm such as hyperhidrosis, vasoconstriction and vasodilation. Trophic skin changes may subsequently develop, including atrophy, scaling, nail changes and contracture of the fascia. Radiographs usually show extensive osteopenia.

The pathogenesis is unknown but may relate to neuroregulatory dysfunction in the autonomic innervation to the arm. Predisposing conditions include age older than 50 years, immobilization following trauma or myocardial infarction, neurologic disorder such as stroke, brain abscess and spinal cord lesions and, interestingly, pulmonary tuberculosis and the use of isoniazid. Although treatment is controversial, the mainstays of therapy are adequate analgesia and intensive physical therapy as soon as possible to preserve function and motion. A short course of prednisone taken orally, starting with 30 or 40 mg twice a day and tapering over four to six weeks, appears to be very beneficial.

Arthritis

Severe pain and degenerative changes in the glenohumeral joint should arouse suspicion of calcium pyrophosphate deposition disease (pseudogout), not primary osteoarthritis, which rarely develops in this joint. Mild degenerative changes in the AC and glenohumeral joints are often visible on x-ray films, but they are rarely symptomatic. When more advanced degenerative arthritis of the AC joint does develop, symptoms may appear. A patient usually has local pain over the joint or pain in the anterior part of the shoulder made worse by shrugging or lifting the hands over the head. A physical examination may show a painful arc between 140 and 180 degrees of abduction, much higher than in patients who have inflammation in the rotator cuff tendons. Findings on radiographs usually confirm the presence of degenerative changes in the AC joint. Treatment of AC joint arthritis usually consists of analgesic and nonsteroidal antiinflammatory agents, reduction of stress applied to the shoulder and physical therapy to maintain full range of motion of the shoulder.

Summary

Clinicians must be aware that on some occasions other important conditions may be responsible for shoulder pain. For example, gallbladder disease or diaphragmatic irritation on the right side may be referred to the upper border of the right scapula. In addition, it should be remembered that the pain of myocardial infarction may be felt most intensely in the region of the left shoulder, usually with some radiation down the inner aspect of the left arm. In most cases a thorough clinical evaluation together with radiographic studies in selected patients will yield the diagnosis and allow a physician to proceed with a rational management plan.

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A Model Poison Control System

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Responding to the need for a poison information, education, data collection and research resource in California's Bay Area and North Coast counties, the San Francisco Bay Area Regional Poison Control Center has become an integral part of the region's emergency medical services. In the first 33 months after it opened, more than 54,000 calls for assistance were received, nearly a third from medical professionals. Through the cooperation and collaboration of public, private and university resources and interests, a cost-effective, comprehensive and accessible system has evolved for public and professional use. Through our experience a system has developed that can serve as a model for poison information services throughout the western states. Emerging public concern for toxicology issues will continue to refine this model.

THE FIRST POISON CONTROL CENTER was established in Chicago in 1953. Since then more than 600 poison control centers have been set up throughout the United States. At first the range of capability of poison control centers was quite variable and depended on the experience and education of staff. Users were often concerned by the lack of medical treatment or toxicology referral assistance. In some cases several centers could be found in the same area, while in other regions large geographic areas remained unserved. In some centers there was no direct medical supervision available. Organization, staffing and range of services offered were not always consistent with the needs of the public and professional communities.

Recently there have been efforts to improve the quality of poison information services. Model systems, based on 30 years' experience in poison control activity, are currently being developed. This report outlines one system that is widely used in northern California. We expect that this model will continue to evolve according to changing professional and community needs.

Development of San Francisco Bay Area Poison Center

In 1973 the National Emergency Medical Services System Act enacted by Congress mandated a comprehensive "systems approach" to organizing critical care systems for handling burns, trauma, spinal cord injury and cardiac, newborn, psychiatric and poisoning emergencies. In the San Francisco Bay Area health agencies responsible

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ABBREVIATIONS USED IN TEXT

SFBA-PCC = San Francisco Bay Area Regional Poison Control Center
UCSF = University of California, San Francisco

for planning and implementing emergency medical services began to develop these systems. Previous attempts to provide public access to poison information and referral assistance had been limited. Service providers wanted an accessible and comprehensive poison information and referral assistance service that could complement the existing network of staffed and equipped treatment facilities in the region. Attention was directed to the needs for thoughtfully designed public education activities aimed at prevention, health professional education programs focused on the recognition and management of poisoned patients and an efficient system for collecting and disseminating regional poisoning experience data.

With the encouragement of local health agencies, the University of California, San Francisco (UCSF), School of Pharmacy proposed in 1978 to establish a poison information center that would serve the San Francisco Bay Area. Faculty from the School of Pharmacy, in collaboration with members of the School of Medicine, had ongoing instructional, research and patient care activities specifically related to clinical toxicology, substance abuse and poison prevention. Their expertise was used in the development of the San Francisco Bay Area Regional Poison Control Center (SFBA-PCC).

To estimate the population to be served by the center, statistics were collected from similarly designed poison control centers in California, Arizona, Utah, Massachusetts and Colorado. The main geographic area served by the San Francisco Bay Area poison control center has a population base of nearly 4 million. Service to several other counties in the less densely populated northwest region of California brings this figure to 4.5 million. With toll-free telephone service the center expected to receive 35,000 to 40,000 calls a year.

The SFBA-PCC is located in the Emergency Department at the San Francisco General Hospital Medical Center, a circumstance that enables the center to provide intensive supportive care. Consultant services such as clinical pharmacology, endoscopy, hemodialysis, peritoneal dialysis and extracorporeal hemoperfusion are readily available. Immediate access to analytical toxicology and clinical laboratory services is available 24 hours a day.

The operational procedures of the center conform to guidelines established by the American Association of Poison Control Centers. Policy and procedures also reflect the recommendations of consultants in the areas of diagnosis, treatment, communication and education.

The following major program goals were established for the poison control center:

- To serve as a resource for the community and to make poison information, treatment and referral more accessible to the public.
- To decrease the number of poisonings and teach the public what to do when poisonings occur.
- To educate and train physicians and other health care providers in the recognition and management of poisoned patients.
- To act as a site for poison research and collect data on instances of accidental poisonings, toxic environmental or occupational hazardous materials exposure.
- To develop research activities that would examine critical clinical problems in toxicology and contribute to their resolution.
- To assess the cost effectiveness and health care impact of poison control services and poison prevention education.
- To offer supervised clinical experience in toxicology to health professional students as a university-based program affiliated with the disciplines of medicine, pharmacy and nursing.
- To be involved in the planning for public and private support of poison information services.
- To encourage the development of legislative authority to provide a statewide geographically balanced network of poison confirmation services, operating in accordance with established standards.
- To provide responsible local, state or national public health and safety agencies information on unique cases, special hazards or unusual causes involved in any poisoning situation.

The SFBA-PCC Model

Staffed 24 hours a day, 7 days a week, 365 days a year, the poison control center is reached through a local San Francisco area number—(415) 666-2845—as well as a toll-free number—(800) 792-0720—for northern California calls

outside the area. The staff of the center currently includes the medical director, an internist with medical toxicology and occupational medicine specialty boards; the program director, a clinical pharmacist, and six PharmD (doctor of pharmacy) trained and experienced toxicology pharmacists as full-time specialists who provide primary telephone consultation on acute or chronic poisoning exposures, drug reactions, drug abuse and overdoses, toxic occupational and environmental hazards, and referral for diagnosis and management of poisonings. There is a laboratory for toxicologic analysis.

In the case of a poisoning, the problem is assessed and the caller given information on the need for treatment, appropriate first-aid measures and whether or not the patient should be taken to an emergency facility or be seen elsewhere by a physician for additional care. Patients are either referred to their physician or to the nearest emergency facility. If a patient is referred, the staff will attempt to call ahead to alert a physician or facility staff of the problem and to provide information regarding the nature and management of the poisoning. If a patient can be managed at home, the staff person instructs the caller and maintains follow-up telephone contact until it is apparent the patient has recovered. The poison control center will also provide on request educational materials on poison prevention, first aid and home safety.

For medical professional inquiries, physician and specialist consultation is available. These consultations are given by telephone and, occasionally, in person. The center also can provide medical professional access to a broad range of information and expertise through its consultants—environmental and industrial toxicologists with the California State Department of Industrial Relations' Occupational Health and Safety Administration (OSHA) and the state's Department of Health Services' Hazard Evaluation System and Information Service; mycologists from the San Francisco Mycological Society; herpetologists, entomologists, botanists and marine biologists and hazardous waste management specialists from local, regional and statewide institutions and agencies. The poison control center refers complex diagnostic and management problems to UCSF faculty in medicine or surgery specialties who have agreed to be consulted on these occasions. Ophthalmologists, cardiologists, nephrologists, gastroenterologists and trauma surgeons are among the clinical specialists to whom the center refers calls for consultation. UCSF faculty physicians in the Emergency Department and the Department of Medicine at San Francisco General Hospital Medical Center are also conveniently available to the poison control center for consultation.

The center has extensive information retrieval capabilities to support its activities. These include a microfiche system (POISINDEX), access to an off-line computer connected to several toxicology data banks, an extensive library of reference materials in medical toxicology, hazardous materials management and pharmacology and a registry of cases having exceptional clinical instruction value. All sources are readily accessible to faculty, staff and students. A computerized case file is currently being developed for instructional purposes.

The poison control center also serves as a backup resource for drug information during evenings and weekends when the UCSF service is normally closed. The center is able to respond to questions from medical professionals that require immediate attention such as drug or product identification, drug-drug interactions or drug-laboratory tests, intravenous-admixture incompatibilities, dose and route of administration of specific drugs and side effects and adverse reactions to drugs. Other types of questions requiring extensive research are usually deferred until the regular service is available.

In 1980 the poison control center, as a member of the San Francisco Fire Department Hazardous Materials Team, became the designated focal point for alerting treatment facilities and public safety agencies of possible dangers and appropriate courses of action in emergencies that arise from fires, spills and other incidences of exposure to toxic and hazardous materials. It does not recommend specific testing, containment, decontamination or disposal procedures, but refers the calling party to the appropriate agencies for these services. With the assistance of the State Division of Occupational Safety and Health Administration, Department of Industrial Relations, the center is compiling a rapid-access technical listing of hazardous materials with information on their chemical nature and safeguards to be used in their handling and decontamination.

In addition to information and referral services the faculty and staff of the poison control center also successfully carry on a variety of research projects. These include studying the effects of repeated oral administration of activated charcoal

in the treatment of acute overdoses, toxin induced seizures and the benefits of particular dialysis procedures, identifying unique toxins in overdose (oleander, 2,4-D [a white crystalline compound, $C_8H_6Cl_2O_3$, used as a weed killer], caffeine, colchicine and so forth) and developing new methods of managing critically overdosed patients.

Professional Education

The poison control center's education program for health care professionals provides instruction in diagnosis, management and follow-up care of patients who have a toxic reaction. Programs are directed toward students from the UCSF Schools of Medicine, Pharmacy and Nursing; residents and fellows in the specialties of pharmacy, emergency medicine, family practice, clinical pharmacology and occupational medicine, and continuing education for physicians, nurses, pharmacists and others. During the year these persons receive supervised clinical experience at the poison control center. In addition, the center publishes a newsletter and cosponsors lectures, conferences and an annual symposium on "The Recognition and Management of Poisonings and Toxicological Emergencies."

Public Education

The center conducts extensive community education programs on poison prevention designed to decrease the incidence of poisonings. Particular emphasis is placed on educating the public about storage and handling of drugs and household chemicals, encouraging the use and understanding of safety packaging, providing readily available data on emergency measures to be followed in case a poisoning occurs and methods of access to specific information on the poison prevention services. Numerous appearances at community health fairs and on television, radio broadcasts, newspapers, schools, churches and shopping centers were made by the center's faculty and staff.

Data Collection—The Expanding Role

Our center collects demographic and epidemiologic information that is used to elicit trends in poisoning occurrences, to assist in determining patterns of use of the service, to support public and professional education activities and to identify new areas of toxicology in which its services have begun to play a key role. The data collection system involves documenting all inquiries handled by the staff. Tabulating and reporting this experience is done every quarter.

In the first year of operation the San Francisco Bay Area poison control center received 13,000 telephone inquiries for information or treatment referral. A total of 70 percent of these calls involved a circumstance where an accidental exposure or ingestion of a potentially poisonous or toxic substance had taken place. Of these incidents, 54 percent involved children younger than 5 years of age. Nearly a third of the requests

TABLE 1.—*Poison Information Requests Received by the San Francisco Bay Area Regional Poison Control Center by Substance—February 1, 1979, Through October 31, 1981*

Agent Involved in Poisoning	*Inquiries (percent)*
Drug*	34.9
Nondrug chemical†	14.5
Plants‡	11.9
Nontoxic§	7.6
Cleaning/household	7.4
Petroleum distillate‖	5.6
Pesticide¶	6.2
Detergent or shampoo	4.1
Toxic fumes or gases	3.2
Cologne or perfume	2.8
Venom	1.8

*Prescription, over-the-counter and street drugs and vitamins and minerals.

†Laboratory, industrial or miscellaneous chemicals and agents not used for medicinal purposes and food.

‡Household, outdoor/garden, mushrooms.

§Listed by POISINDEX as nonpoisonous; active ingredient and other ingredients in concentrations considered to be nontoxic.

‖Gasoline, furniture polish, paint remover, and so forth.

¶Insecticides, herbicides, rodenticides.

TABLE 2.—*Calls Received by San Francisco Bay Area Regional Poison Control Center by County of Origin, February 1, 1979, Through October 31, 1981*

County	*Percentage of Total Calls*
Alameda	12.3
Contra Costa	11.0
Del Norte	0.05
Humboldt	3.2
Lake	0.8
Marin	9.8
Mendocino	1.8
Monterey	1.4
Napa	1.2
San Francisco	36.2
San Luis Obispo	0.2
San Mateo	11.0
Santa Clara	2.2
Santa Cruz	0.5
Solano	1.2
Sonoma	1.0
Other	3.4
Unknown	2.6
Out of state	0.2

were considered professional calls for information and help from either a physician or a nurse at hospitals and offices in northern California. In addition, all of the acute care hospitals in the area had used the center, some as frequently as 50 to 100 times during the first 12 months. In February 1981, at the beginning of 24 months of continuous activity, the total number of calls received by the poison control center reached 31,000. As of January 1, 1982, the total cumulative number of inquiries was 50,000. The proportion of calls from medical professionals remained at the 30 percent level throughout the 33 months covered in this report.

In all, 63 percent of calls originate from a private residence and 22 percent from an emergency room; 8 percent are environmental in nature or from a workplace and 4 percent from a physician's office. Of the total number of calls received, 69 percent pertain to an actual exposure that has caused acute symptoms, 57 percent involve children 5 years of age or younger and 35 percent involve persons older than age 17. About 81 percent of the exposures are by ingestion, 7 percent by inhalation, 5 percent by skin contact and 4 percent by eye contact. Envenomation is responsible for exposure 2 percent of the time.

During the period from February 1, 1979, to October 31, 1981, of the 21,740 calls for help where an actual poisoning exposure or ingestion occurred at home, referral to a physician, emergency room or hospital was made 22 percent of the time. About 78 percent of the cases, or 16,989 calls, were initially managed at home. Syrup of ipecac was available and administered at home in 9 percent of these cases. Poisonings occur with a variety of agents (see Table 1). Five counties represent the point of origin of nearly 75 percent of all the calls (see Table 2) during this 33-month period.

A prospective review of telephone inquiries received by the poison control center staff during a six-month period in 1981 (June through November) has identified increasing concern in the area of occupational toxicology. Questions or problems arising from workplaces, from public safety officers exposed to toxic spills or from workers transporting products accounted for 226 calls (2 percent) received during the survey period. Use of the center's services by medical personnel, particulary emergency room physicians, was substantial during this time. Because medical schools in the United States devote only a small portion of undergraduate training time to occupational medicine,[1] most physicians have limited knowledge in occupational toxicology and are faced with an increasing number of industrial chemicals and unfamiliar workplace activities. For emergency room physicians, these problems are compounded by the need to make rapid treatment decisions. The poison control center's services were a useful resource to medical personnel with occupational medical questions during the survey period.

Demographic and epidemiologic data collection and study by the center have also elicited more efficient ways of handling toxicologic emergencies. Calls were received during three major chemical incidents in the San Francisco Bay Area in 1981: aerial spraying of malathion, a silicon tetrachloride spill and a polychlorinated biphenyl/methane gas leak. In each of these situations, the center's services were sought mainly for information. Review of the number and type of calls received indicates that toxicologic emergencies can best be managed when a central institution disperses information to medical facilities, public safety officers, the public and the press. Coordinated decontamination efforts, including mobile units, would be extremely useful. In addition, during an environmental crisis, information lines at the center must be kept open for people with other types of emergency calls. While providing an effective resource during chemical emergencies, poison control centers must be able to continue efficiently handling their other services.

In addition to its traditional focus on the prevention and treatment of accidental ingestions and acute drug overdoses, the San Francisco Bay Area Regional Poison Control Center has expanded its services and is now providing occupational and environmental toxicologic information to the public, medical personnel, public safety officers and the press. Poison control centers can assume a vital role in the efficient handling of such questions and referrals.

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Medical Evaluation Before Operation

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Surgical outcome can be optimized by anticipation and prevention of medical complications. General considerations that apply to all patients include evaluation for coagulation disorders, prior anesthetic complications and drug history.

Evaluation for organ-specific risk factors allows identification of patients at high surgical risk, minimization of risk and anticipation of postoperative complications. Review of the recent literature and a practical guide to therapy is presented for the major medical considerations before surgical procedures: cardiac disease, hypertension, pulmonary disease, endocrine considerations and hepatic disease. Attention to these areas and communication among internists, anesthesiologists and surgeons should provide optimal treatment of surgical patients with medical disease.

IMPROVED anesthetic and surgical techniques have made it possible to safely operate on patients with preexisting medical problems. Successful management requires communication and cooperation among surgeons, anesthesiologists and internists during the perioperative period. Within the last several years, an expanding literature in medical, surgical and anesthesiology journals advises physicians on assessment of risk, medical aspects of preparing for surgical procedures, and anticipation and prevention of medical complications in surgical patients. In this paper we review the recent literature and provide an approach to perioperative medical management based on our experience with a general medicine consultation service at a university hospital.

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General Considerations

Operative mortality for a healthy patient having an elective procedure is approximately 1 in 10,000.[1] The risk is minimized by attention to three areas of the history: coagulation disorders, drug history and previous anesthetic complications.

Information should be obtained about any earlier episodes of postoperative or postpartum bleeding, spontaneous bleeding, family history of coagulation disorders and recent ingestion of aspirin or nonsteroidal antiinflammatory agents. Routine preoperative laboratory evaluation includes a prothrombin time, partial thromboplastin time and platelet count; however, even if these values are normal, further evaluation should be carried out in a patient with a history suggesting a coagulation disorder. A test of bleeding time should be done next. A normal platelet count and a prolonged bleeding time suggest a qualitative platelet disorder such as in von Willebrand's disease or aspirin ingestion. Diagnostic evalua-

ABBREVIATIONS USED IN TEXT

CHF = congestive heart failure
CPK = creatine phosphokinase
ECG = electrocardiogram
FEV_1 = forced expiratory volume in one second
FVC = forced vital capacity
HBsAg = hepatitis B surface antigen
IPPB = intermittent positive pressure breathing
P_{CO_2} = carbon dioxide partial pressure (tension)

tion in patients with coagulation disorders has been recently reviewed,[2] and surgical management of patients with the common coagulation disorders has been discussed.[3-5]

Of unexpected bleeding complications during surgical procedures, 80 percent are due to unappreciated aspirin use, and bleeding time should be determined in any patient who has recently ingested aspirin or a nonsteroidal antiinflammatory agent.[6] The prolongation of the bleeding time seen with aspirin varies; in most patients bleeding time will still be within normal limits. Some patients will have a significantly prolonged bleeding time, however, and prolonged bleeding time and an operation in which hemostasis is difficult to achieve are indications for postponing an operation. If surgical intervention cannot be postponed, a platelet transfusion should be given.

Many drugs interact with anesthetic agents, and a history of recent administration of these drugs may affect choice and dosage of anesthetic agents. Succinylcholine chloride is potentiated by antibiotics (particularly aminoglycosides and clindamycin),[7] lithium,[8] quinidine,[9] echothiopate iodide (phospholine eyedrops),[10] cyclophosphamide,[11] other antineoplastic drugs[12] and diethylstilbestrol.[13] The interaction of anesthetic agents and drugs has been reviewed.[14-16]

Patients should be queried about a personal or family history of anesthetic complications. Attention should be given to a history of postoperative jaundice and, if obtained, records should be reviewed to ascertain whether jaundice was associated with halothane administration. Halothane should not be readministered to a patient with a history of halothane-associated hepatitis.[17]

A history of prolonged apnea following anesthesia suggests pseudocholinesterase deficiency. This is an autosomal recessive disorder with an incidence of approximately 1 in 2,500. In any patient with a suggestive history, pseudocholinesterase deficiency can be shown by serum tests for enzyme activity.[18]

Malignant hyperthermia is an autosomal dominant disorder of skeletal and myocardial muscle metabolism and has an incidence of about 1 in 20,000.[19] Affected patients are generally asymptomatic, but with provocation with succinylcholine and a volatile anesthetic the abnormality is induced. Intracellular calcium content is increased, which results in cellular hypermetabolism, acidosis and the biochemical abnormalities of rhabdomyolysis. In any patient with a family history of anesthetic-induced hyperthermia or sudden unexplained anesthetic death a serum creatine phosphokinase (CPK) determination should be done. The CPK level is elevated in approximately 70 percent of patients with malignant hyperthermia. A positive family history and an elevated enzyme level are sufficient evidence to consider a patient susceptible. If a patient has a positive history but a normal CPK level, a muscle biopsy with in vitro testing is needed to further substantiate the diagnosis.[19] Recently, dantrolene sodium has been given orally preoperatively to prevent malignant hyperthermia[20] but failures have been reported.[21] Patients with malignant hyperthermia require careful anesthetic management with facilities immediately available to treat any complications.[22]

Two further preoperative considerations that apply to all patients are nutritional assessment and psychologic preparation for operation. Malnutrition is prevalent in certain groups of patients: alcoholics,[23] the elderly[24] and those admitted to hospital for medical disease.[25] Several measures have been used to assess nutrition: height-to-weight ratio, arm circumference and skin-fold thickness, serum albumin level, serum transferrin concentration, skin test delayed hypersensitivity and grip strength.[26-28] For an individual patient, however, a careful history and physical examination provide a good index of nutritional state.[28] Attention to nutritional state may decrease surgical morbidity.[29-31]

Although most preoperative counseling will be done by surgeons, primary care physicians have a role in the psychologic preparation of patients. Providing patients with information about what to expect and coping techniques for the postoperative period has been shown to reduce pain medication requirements and to shorten hospital stays.[32]

The Dripps classification categorizes patients according to the overall severity of their disease (see Table 1) and correlates with operative mortality.[33] Additionally, the type of surgical procedure affects morbidity and mortality: transure-

thral prostatectomies are low risk[34]; operations on the extremities and intra-abdominal and intrathoracic procedures have increasing risk,[35] and risk is increased in older patients[36] and during emergency operations.[35] The type of anesthesia does not relate to anesthetic risk.[37,38] The Dripps or American Society of Anesthesiologists classification gives no specific criteria on how to judge the severity of a patient's illness. However, by studies for organ-specific complications in patients, physicians may more accurately identify those at highest surgical risk, minimize that risk and avoid surgical morbidity.

Cardiac Disease

The presence of cardiac disease is a predictor of operative morbidity and mortality and it is responsible for approximately a third of operative deaths.[39] In 1977 Goldman and co-workers[40,41] published a prospective study of approximately 1,000 patients evaluated for cardiac risk factors. Factors affecting risk along with their relative importance are shown in Table 2. At highest risk were patients with uncompensated congestive heart failure (S3 gallop or jugular venous distension) and patients with a myocardial infarction within the last six months. Additional risk factors were signs of aortic stenosis, age older than 70 years, any rhythm other than sinus rhythm and several laboratory values indicating organ system disease (high carbon dioxide partial pressure [P_{CO_2}], serum creatinine level over 3 mg per dl or signs of chronic liver disease). Information from history, physical examination and laboratory evaluation was assigned a point score that correlated with cardiac complication rate. Other investigators have confirmed the predictive value of these cardiac risk factors.[42] Factors that did not correlate with cardiac risk were smoking, hypertension, stable angina (though the subset of the New York Heart Association class IV angina contained too few patients to be evaluated), mitral valve disease, cardiomegaly or conducting system disease.[40,41]

Patients with congestive heart failure (CHF)

TABLE 1.—*American Society of Anesthesiologists (Dripps) Classification for Surgical Risk*

1. Healthy; elective procedure
2. Mild to moderate systemic disease
3. Severe systemic disease, limits activities but not incapacitating
4. Life-threatening disease
5. Moribund and not expected to live without surgical intervention

TABLE 2.—*Cardiac Risk Factors and Classification of Risk**

Means of Evaluation	*Finding*	*No. of Points*
History	Myocardial infarction 6 months before operation	10
	Age >70	5
Physical examination	S3 gallop or jugular venous distension	11
	Signs of aortic stenosis	3
Electrocardiogram (ECG)	Any rhythm other than sinus rhythm or premature atrial contractions on last preoperative ECG	7
	More than 5 premature contractions per minute on any previous ECG	7
Laboratory data and general status	P_{O_2} <60 or P_{CO_2} >50 mm/mercury, potassium <3.0 or HCO_3 <20 mEq/liter, BUN >50 or creatinine >3.0 mg/dl, abnormal AST, signs of chronic liver disease or patient bedridden for noncardiac causes	3
Operation	Emergency surgical treatment	4
	Intraperitoneal, thoracic or major vascular procedure	3
	TOTAL	53

Class	*No. of Points*	*No. of Minor Complications (percent)*	*Life-Threatening Complications (percent)*	*Cardiac Death (percent)*
I	0-5	99	0.7	0.2
II	6-12	93	5.0	2.0
III	13-25	86	11.0	2.0
IV	26	22	22.0	56.0

*Reproduced from Goldman et al[40] as modified by Salem et al[39] with permission of the authors and publishers. AST = aspartate aminotransferase (formerly SGOT), BUN = blood urea nitrogen, HCO_3 = the bicarbonate radical, P_{CO_2} = carbon dioxide partial pressure (tension), P_{O_2} = oxygen partial pressure (tension).

should be treated optimally before a surgical procedure. Because physical examination underestimates the degree of congestive failure, some authors suggest preoperative hemodynamics measurement to assess for the presence of failure.[43] Patients with CHF are at increased risk of postoperative exacerbation of their failure, half of which is due to excessive intraoperative fluid administration.[44] In these patients careful fluid management is required perioperatively.

Stable angina is not a contraindication to an operation; therapy with propranolol (see further discussion below) and nitrates should be continued preoperatively and resumed postoperatively. If a history of myocardial infarction is obtained, an elective surgical procedure should be postponed until six months following infarction.[45] If evidence of an old infarction is found on electrocardiogram (ECG) without a history of chest pain, an old ECG should be obtained. If an old ECG is not available, it is prudent to delay surgical procedure three months.[39] Patients who have had coronary bypass grafting generally do well during subsequent surgical procedures a month or more following their bypass.[46,47]

In general, temporary ventricular pacing during a surgical procedure is rarely indicated unless there are indications for permanent pacing. Bundle branch blocks and bifascicular blocks are not indications for prophylactic placement of a temporary pacemaker. Patients with conducting system disease are at increased surgical risk, but the risk is due to coincident myocardial disease rather than conducting system disease.[39] These patients should be monitored; and atropine sulfate, epinephrine and isoproterenol hydrochloride must be available. Patients with permanent pacemakers require monitoring in surgery, especially while cauterizing units are in use. Should the pacemaker be suppressed by external current, magnets to change from demand to fixed rate mode must be available.

Ventricular and atrial premature contractions are an index of underlying cardiac disease.[40] Patients with these abnormalities should be monitored and given antiarrhythmic medications if more complex arrhythmias or hemodynamic compromise occurs; prophylactic therapy is not recommended.

Aortic valvular disease is a cardiac risk factor.[39] Echocardiography should be considered in preoperative evaluations in patients with systolic ejection murmurs to identify aortic stenosis and asymmetric septal hypertrophy associated with hypertrophic subaortic stenosis. Both disorders require careful perioperative fluid management. Inadequate fluid replacement and asymmetric septal hypertrophy may precipitate increased left ventricular outflow obstruction and decreased cardiac output, which would be further exacerbated by the use of inotropic agents. Endocarditis prophylaxis should be given for accepted indications.[48,49]

Patients with prosthetic valves receiving anticoagulants require careful management. For minor surgical procedures (dental extraction, pacemaker battery change), anticoagulation therapy may be briefly discontinued while the prothrombin time decreases to less than 15 seconds and then restarted immediately postoperatively.[50] Prosthetic valve location affects risk of thromboembolic events. Retrospectively, patients with aortic valve prostheses had less embolic disease than patients with mitral valve prostheses.[51] For major surgical procedures, patients with aortic prostheses should have sodium warfarin therapy discontinued briefly, their prothrombin time allowed to return to normal preoperatively and the warfarin therapy restarted postoperatively. Patients with mitral valve prostheses should receive vitamin K parenterally 24 hours preoperatively to allow the prothrombin time to reach normal interval, full continuous intravenous administration of heparin should be begun 12 hours postoperatively, warfarin therapy resumed when the patient is taking oral medications and heparin given continuously until the prothrombin time on warfarin administration is therapeutic for five days.[52] The choice among various methods of managing anticoagulation can be determined for each patient.[53]

Hypertension

Hypertension alone is not a risk for cardiac complications from a surgical procedure,[39] but it is often associated with coexisting cardiovascular disease. When evaluated prospectively, surgical risk in patients with mild diastolic hypertension (a diastolic blood pressure of less than 110 mm of mercury) was not increased when controlled for surgical procedure and other underlying disease.[54] Surgical procedures in patients with higher elevations of blood pressure should be postponed until the blood pressure is lowered. All hypertensive patients require careful intraoperative and postoperative blood pressure management.

In general, antihypertensive medication should be continued before an operation. Potassium in

patients taking diuretics should be adequately repleted before a surgical procedure to prevent hypokalemia-associated cardiac arrhythmias.[55,56] The serum potassium measurement is an insensitive indicator of total body potassium content. A serum potassium level of 3.0 mEq per liter predicts a total body potassium deficit of approximately 300 mEq. Potassium values should be normal (more than 3.5 mEq per liter) before an operation. Adequate repletion of potassium stores may require several days and necessitate a delay in operation.

Initially it was felt reserpine therapy had to be discontinued several weeks preoperatively to prevent blood pressure lability during anesthesia.[57] It is now recognized that reserpine administration can be continued preoperatively and resumed postoperatively when the patient is taking medications orally.[58]

Concern has been voiced regarding whether propranolol therapy should be continued before a surgical procedure. It was feared that a β-blocking agent would impair vascular reflexes and cardiac performance.[59] Conversely, propranolol withdrawal has been associated with "propranolol rebound," a state of adrenergic excess and, consequently, an increased incidence of angina.[60] The mechanisms of this "rebound" have been discussed.[61] It now appears that propranolol therapy can be continued safely preoperatively and resumed immediately postoperatively. Goldman[62] has presented recommendations for perioperative management of patients receiving propranolol for hypertension or coronary artery disease.

Clonidine hydrochloride is only available for oral administration; its effects dissipate over 24 to 36 hours. Discontinuation of clonidine therapy has been associated with rebound hypertension.[63] In general this occurs in patients receiving large doses of clonidine (more than 2 mg a day), but it has occurred with lower doses. If oral administration of medications can be resumed immediately following the surgical procedure, clonidine therapy can be continued. Otherwise, a patient should be switched to another antihypertensive drug before the operation. Tapering clonidine doses over several days reduces the incidence of rebound hypertension.[64] Hydralazine hydrochloride or methyldopa therapy does not present problems in management as either is available for parenteral use and may be continued preoperatively and resumed immediately postoperatively.

Pulmonary Disease

Pulmonary risk factors for surgical procedures have been reviewed.[65] Anesthesia, medications, bandages and immobilization in a supine position all adversely affect respiratory function. Functional residual capacity, tidal volume and the number of sighs decrease postoperatively,[66-68] and "miliary atelectasis," ventilation-perfusion abnormalities and hypoxia develop.[69] In addition, pulmonary defense mechanisms are impaired because of decreased mucociliary transport.[70] The major postsurgical pulmonary complications are atelectasis and infection.

Factors besides pulmonary disease that predict increased pulmonary risk include the following: site of operation (thoracic surgical procedures having highest risk),[71] smoking,[71] obesity[72] and age older than 60 years.[73] Obese patients have decreased lung volumes that are further reduced by surgical procedures and the supine position. They are at increased operative risk, require unique anesthesia management[74] and should be advised to lose weight before an elective procedure.

Many investigators have tried to define how to best use pulmonary function tests to delineate pulmonary risk. Maximum breathing capacity has the best predictive value; it is an overall index of lung function, respiratory muscle strength and patient cooperation.[75] High pulmonary risk is predicted by a forced expiratory volume in one second (FEV_1) of less than 2 liters and FEV_1/FVC (FEV_1/forced vital capacity) of less than 70 percent of predicted.[76-78] An elevated P_{CO_2} or large amounts of sputum production are also adverse factors.[76,77]

Several preoperative measures can minimize pulmonary risk. Education in the use of the incentive spirometer and breathing exercises will increase compliance in postoperative maneuvers.[78] The goal of the incentive spirometer is to reverse atelectasis, which is best accomplished with maximum inspiration with an open glottis.[79] Many models of incentive spirometers are available; they are equivalent in prospective studies.[80] For the instrument to be used correctly, a patient must take a maximum inspiration and hold it for two to three seconds; this must be done ten times an hour while a patient is awake.[80] Intermittent positive pressure breathing (IPPB) has been evaluated in many studies; it offers no advantages over the less expensive and safer incentive spirometers.[81-83]

Patients should be advised to discontinue

smoking before an operation. Improvement in pulmonary function requires several weeks, but even immediate preoperative cessation of smoking will decrease the carboxyhemoglobin level and improve mucociliary transport.[84,85]

Preexisting reversible bronchial obstruction and respiratory tract infection should be treated before an operation. Surgical procedures in patients with chronic bronchitis should be done late in the day to allow morning mobilization of sputum. Intravenous hydration and parenterally administered bronchodilators should be given if acute reversal of airway bronchospasm is required or if a patient continually uses bronchodilators and cannot take medications orally. Because of arrhythmogenic potential, serum theophylline concentrations should be monitored.

Review of postoperative pulmonary management suggests no treatment is better than an aggressive "stir-up" regimen of turning, coughing, deep breathing and early ambulation.[86] The use of the incentive spirometer has been described.

Minidoses of heparin, administered subcutaneously, are used in selected situations for the prophylaxis of venous thromboembolic disease. In general surgical procedures, minidose heparin therapy (5,000 units subcutaneously) is indicated for any patient more than 40 years old with no history of bleeding disorders, normal coagulation studies and no aspirin use for ten days. Sodium heparin is administered two hours before an operation and at subsequent 12-hour intervals until a patient is fully ambulatory or discharged.[87] Calcium heparin, recently available in this country, is given on an eight-hour dosage interval.[88] Minidose heparin therapy is not useful for major orthopedic procedures, open prostatectomies or active thromboembolic disease. Because of the potential severe adverse effects of bleeding complications, it has not been evaluated in surgical treatment of the eye, spinal anesthesia or neurosurgical procedures. The cost effectiveness of the various methods of thromboembolic disease prophylaxis in surgical patients has been reviewed.[89]

Endocrine Disease

Management of diabetes, thyroid disease and prior steroid therapy are the most common preoperative endocrine considerations.[90] Many methods have been suggested to treat diabetic patients undergoing a surgical procedure. These recommendations have been tabulated by Alberti and Thomas.[91] Approaches have not been compared prospectively, and treatment must be specific for each patient. Schemes for glucose control are presented in Table 3. Intraoperatively, the serum cortisol level and that of other counterregulatory hormones increase, and hypoglycemia is rare.[92] If the operation lasts more than three hours, an intraoperative glucose level should be monitored. Constant infusion of insulin is becoming a preferred method for management of diabetic patients.[93] Patients with mild glucose intolerance or those using agents orally may be best managed with "sliding scale" subcutaneously administered regular insulin based on serum glucose levels. Chemstrip-bG Blood Glucose Tests (Bio-Dynamics, Indianapolis, Ind.) and other methods for rapid serum glucose level determination make serum glucose monitoring practical. Sliding-scale coverage based on urine glucose reductions should be abandoned.[94] Many drugs interfere with these urine determinations,[95] and the serum glucose level is now preferable. Diabetic patients have a higher incidence of postoperative cardiac and infectious complications; they require careful follow-up for these potential problems.[96]

Uncorrected hypothyroidism is a contraindica-

TABLE 3.—*Perioperative Regimen for Diabetic Patients*

Management with intermediate-acting insulin therapy given subcutaneously

1. Bedtime snack the night before, with early morning operation
2. Five percent dextrose in water solution (D5W) begun morning of operation and continued during and after operation
3. A third to half usual dose of intermediate-acting insulin given on morning of operation and again in the recovery room

Management with constant infusion of regular insulin

1. Nothing by mouth after dinner the night before operation
2. Begin infusion of D5W solution at 100 to 150 ml/hour at 10 PM the night before
3. Piggyback insulin infusion given intravenously at 0.5 to 1 unit of regular insulin/hour
4. Check serum glucose level every 3 hours and adjust insulin infusion to achieve glucose level of approximately 150 to 200 mg/dl
5. Infusion continued intraoperatively and postoperatively, with adjustments as needed
6. Discontinue infusion therapy when taking 1,000 calories orally a day and resume insulin therapy given subcutaneously

Sliding-scale management

1. D5W solution used intraoperatively
2. Serum glucose level monitored every 6 hours and regular insulin given subcutaneously as needed

TABLE 4. *Perioperative Treatment of Patients With Adrenal Suppression*

Major procedure
1. The night before, hydrocortisone (HC), 100 mg, given at 6 PM and 12 midnight
2. Day of procedure, 100 mg of HC given intravenously during operation and every 6 hours
3. Postoperative day 1, 50 mg of HC given every 6 hours
4. Postoperative day 2, 25 mg of HC given every 6 hours
5. Resume preoperative cortisol therapy, added steroid coverage indicated if complications occur postoperatively

Minor procedure (endoscopy, dilation and curettage, dental surgical procedures)
1. A single 100-mg HC dose given preoperatively
2. An additional 20 mg of HC given the evening of procedure

tion to surgical procedures and is associated with postoperative hypotension, prolonged sedation, hypoventilation[97] and hyponatremia.[98] If an emergency operation is required, full intravenous replacement using levothyroxine should be done.[97] Coronary bypass procedures in patients with hypothyroidism present special problems that have been recently reviewed.[99,100]

An operation may precipitate a thyroid storm in patients with hyperthyroidism[101] and patients should be made euthyroid before a surgical procedure. Propranolol, iodine, methimazole and propylthiouracil can be used to manage hyperthyroidism before surgical intervention.[102] Propranolol alone is not uniformly successful in preventing thyroid storm,[103] and patients require close monitoring in the perioperative period.

Patients with adrenal suppression require exogenous steroid therapy in surgery and in the perioperative period.[104] Assessment of the hypothalamic-pituitary-adrenal axis using cosyntropin, insulin-induced hypoglycemia or metyrapone has not been done prospectively as a guide to which patients with a history of steroid use should receive perioperative steroid coverage. A conservative approach is recommended; any patient with more than two weeks of continuous steroid therapy in the last six months should receive perioperative steroids. The steroid coverage of these patients is outlined in Table 4.[105]

Hepatic Disease

The importance of a history of postoperative jaundice has been discussed. Additionally, patients with a history of jaundice or abnormal liver function values should have their hepatitis B surface antigen (HBsAg) status determined. Acute viral hepatitis of unknown type, non-A non-B hepatitis or HBsAg positivity are predictions for "blood and needle" precautions outlined in the infection control manual required for hospital accreditation.

Childs classification[106] or its modifications[107] predict operative morbidity and mortality in patients with chronic liver disease. Assuring adequate oxygenation, preventing hypotension and avoiding anesthetics that decrease splanchnic circulation minimize morbidity in these patients.[108,109]

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Refer to: Fox ERW: Commentary from Coeur d'Alene: Care for terminally ill patients (Commentary). West J Med 1982 Oct; 137:359-360

Commentary From Coeur d'Alene: Care for Terminally Ill Patients

E. R. W. FOX, MD, *Coeur d'Alene, Idaho*

"MOST PATIENTS are so old and sick you can't do anything for them. You concentrate on training yourself to help the few who are young and salvageable." These were the words of an intern spoken during an interview with his preceptor, reported in a recent issue of the *Journal of the American Medical Association*.[1] The fledgling physician went on to label the "unsalvageable old and sick" as "dirtballs."

That term grates on our ears. It is pejorative, it lacks the milk of human kindness that should be a part of every physician's makeup. A moment's reflection reminds us, however, that every one of us, as young physicians, too often looked upon sick and dying patients with cold disdain. Out of a feeling of frustration every generation of interns and residents has had derogatory names for old, incurable patients: "gomer," "old crock" or "PMS"—translated, "poor, miserable s.o.b."

A hundred years ago Ralph Waldo Emerson recognized the hopelessness of old age when he wrote, "Nature abhors the old, and old age seems the only disease; all others run into this one."[2]

And 2,000 years ago Seneca made this comment on our limitations as physicians: "Old age is a disease we cannot cure."[3]

Aged, terminal patients, in particular, have been the victims of neglect. As such a patient lies there on his sick bed he is a reminder of our failure to effect a cure, to render another miracle. For our part, when making rounds we pass by his bed as quickly as possible, hurrying on to care for those who are "young and salvageable."

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This attitude of purposeful neglect has given birth to a new movement, a concept devoted to the care of terminal patients. It is called *hospice*. This idea had its beginning in England just a few years ago and is now fast becoming a part of the health care system in the United States. Third-party payors, including state and federal governments, are beginning to look favorably upon this concept. Hospice care of a terminal patient is, in most instances, home care. Using volunteers, the cost of hospice care is a fraction of the cost of hospital care.

Small wonder, then, that the third-party payors are showing interest.

The medical profession has joined in giving tacit support to the hospice movement. Perhaps we are relieved to have someone else take over the onerous task of terminal patient care. This could be another demonstration of how the care of patients is being fragmented. We have given up the after hours house call; the emergency room has allowed us to abdicate this duty. Elder care has been taken over by the nursing home. Now we may, indeed, be at the point of relegating the total care of terminal patients to hospices.

Many volunteers are waiting in the wings, eager to be anointed as "care givers" for the terminally ill. The emotional appeal is there. Nurses, social workers, psychologists, clergy and all manner of health professionals are ready to join the program. Even the morticians are claiming the right to take part in life's terminal event.

The AMA, in testifying before a Congressional subcommittee, recommended that the Medicare program should not at this time cover the cost

of hospice care. There is an understandable uncasiness about how these hospice programs will be administered, how the personnel will be chosen and just how the terminal care will be given.

The AMA has wisely perceived the difficulties that may confront us in the hospice care of terminal patients. Will all volunteers be adequately trained? Arc the guidelines of care well defined? Arc there ethical considerations? Will confidentiality be preserved? What is there to prevent an unscrupulous operator from setting himself up as a hospice?

Legislatures and accrediting agencies on the state and national levels are looking for the answers to these questions. We physicians have an obligation to help find the answers. We owe it to our patients and to our profession.

The "young and the salvageable" will always get the best of care. A hospice in good hands, with physician cooperation and guidance, can bring hope and compassion to terminal patients. The hospice concept, embraced by doctors, both the youthful and the seasoned, could wipe away the stigma of being a "dirtball."

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Heart Transplants

QUESTION:

1. *Are heart transplants now considered standard treatment or are they still considered to be experimental?*
2. *What are the indications for a heart transplant?*

OPINION:

It is the opinion of the Advisory Panels on Chest Diseases, General Surgery and Internal Medicine that

1. At this time, cardiac transplantation cannot be considered standard treatment. It is acceptable treatment when performed by highly qualified transplant units such as those at Stanford University and the Medical College of Virginia.
2. The ideal candidate for a heart transplant is a young, otherwise vigorous person, who is dying of end-stage cardiac disease, who is also optimistic and willing to risk a complex procedure and course for the chance of marked functional improvement. The patient should be between the ages of 12 and 50 years and have a poor prognosis for surviving for more than six months. The heart disease should be irremediable by standard forms of medical or surgical therapy. The patient should evidence psychosocial stability by previous gainful employment and good medical compliance if he or she is to be completely rehabilitated. Contraindications, at the present time, reflect those factors that limit survival or cause postoperative complications, such as diabetes mellitus, active infection, other severe irreversible organ disease, such as renal failure or peripheral vascular disease. In addition, the patient must have fixed pulmonary vascular resistance of less than 5 or 6 Wood units.

BOOK REVIEWS

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

ABDOMINAL RADIOLOGY—Editor: James J. McCort, MD; Authors: James J. McCort, MD; Robert E. Mindelzun, MD; Robert G. Filpi, MD, and Charles Rennell, MD. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD (21202), 1981. 344 pages, $49.50.

The stated purpose of this modest-sized book is to provide radiologists and attending physicians with a step-by-step evaluation of abdominal radiographs in regard to technique, normal anatomy and a host of abnormal radiographic findings. Each chapter focuses on specific topics such as technique, peritoneal and extraperitoneal anatomy, abdominal calcifications, normal and abnormal fluid and gas collection, and abdominal masses. The book is aimed at radiologists, surgeons, internists, family practitioners and emergency room physicians. The text mainly discusses plain abdominal radiographs with introduction of contrast studies, computerized tomography and ultrasound where appropriate to illustrate or confirm findings.

The aims of the authors are well met. The book contains a superb collection of well-reproduced radiographs illustrating an amazing number of entities. In addition, there are many fine drawings and illustrations that are quite useful to explain pertinent anatomy and pathologic conditions. The references provided with each chapter are extensive and appear to contain the key references in the field. This book would provide an excellent start for a literature search for many radiologic findings. The relatively low cost (for a finely illustrated radiology text) is commendable.

The only drawback to the text is the necessarily limited discussion of many topics. The book is ideal for a radiology resident or nonradiologist who needs to be well versed in the technique and interpretation of abdominal radiographs. It is not suited for an experienced radiologist who needs an in-depth reference work. It would be quite useful as a rapid, albeit somewhat limited, guide for looking up a specific point. The references could then be consulted for a more detailed topic discussion. The book also would be an excellent guide for teaching purposes.

In summary, this book can easily be highly recommended as a textbook for radiology residents, and as a reference book for attending physicians who must deal with acute abdominal conditions. Experienced radiologists would also find it useful as a handy quick guide with respect to abdominal anatomy and pathology.

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* * *

BONE METASTASIS—Volume Five in the series: METASTASIS—Edited by Leonard Weiss, ScD, MD, PhD, Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York; and Harvey A. Gilbert, MD, Department of Radiation Therapy, Southern California Permanente Medical Group, Los Angeles. G. K. Hall Medical Publishers, 70 Lincoln Street, Boston (02111), 1981. 512 pages, $55.00.

Bone Metastasis, edited by Weiss and Gilbert, is a wide-ranging work with a large group of contributors. Ordinarily this would mean a lot of redundancy, but not so in this case. Very few things are repeated, yet each chapter can stand alone as an informative article.

The entire spectrum of bone metastasis is covered, including an historical piece, the 1956 Caldwell Lecture by Batson, which has certainly stood the test of time. Much of the book is really in the realm of basic science —anatomical pathways, physiologic and biochemical aspects and laboratory studies. Although these are welcome to researchers in this field, they will not be of much interest to most practicing physicians or residents.

The chapters dealing with the clinical approach to bone metastasis were especially well written and are very readable. Chapter 10, "The Radiologist and the Diagnosis of Bone Metastases" by Schreiber, and Chapter 11, "The Radionuclide Scan in Bone Metastasis" by Low, should be required reading for all radiologists.

The chapter on computed tomographic (CT) scans of bone and soft tissue metastases is very good but, because of the rapidly evolving field of CT, some of the more recent advances have not been mentioned. Also, no mention is made of nuclear magnetic resonance, which promises to be important in tumor and metastasis imaging. Magnification radiology, a very useful imaging modality in metastatic bone disease, is not mentioned either.

Perhaps more should have been said about the proper workup of a patient with bone metastasis—that is, the utility, or lack of utility, of skeletal surveys as opposed to radionuclide scans. When should workups be augmented with CT scans and tomograms? These things were, indeed, briefly mentioned, but not emphasized. This can be a very confusing and, for a patient or bill-payer, costly maze.

These minor criticisms should not hide the fact that this is an excellent work with each chapter containing a complete bibliography and with a full index at the end of the volume. It contains the latest in diagnostic workup, orthopedic advances and therapy. It should be well received by all in this field of medicine.

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OBSTETRIC ULTRASOUND: APPLICATIONS AND PRINCIPLES—Edited by W. S. Van Bergen, MD, Clinical Assistant Professor of Obstetrics and Gynecology, Southern Illinois University School of Medicine, Springfield, Illinois. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1980. 157 pages, $19.95.

This book is clearly written and reduces complex concepts to simple terms. Its contributors include several pioneers and leaders in the field of obstetrical ultrasonography. It is particularly useful to students, residents and practitioners who require a general understanding of the field and knowledge of the usefulness and limitations of the modality. In this sense it has real value and fulfills a genuine need. The chapters on the history of ultrasound, basic principles of diagnostic ultrasound, and the state of knowledge pertaining to safety are interesting and informative.

Since the book is a general overview and not a detailed text, readers should not expect to learn to become proficient in the performance and interpretation of obstetrical ultrasound by studying it. Nor can it be used

as a reference text for the field. In the preface the senior author addressed the need for a short, easily interpreted book designed specifically for practitioners. I believe he has succeeded in producing such a book.

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* * *

CANCER OF THE HEAD AND NECK—Edited by James Y. Suen, MD, and Eugene N. Myers, MD. Churchill Livingstone Inc., 19 West 44th St., New York, NY (10036). 1981, 905 pages, $89.00.

This textbook, edited by Drs. Suen and Myers, is the most comprehensive available pertaining to head and neck cancer. The editors have compiled well-integrated chapters by more than 50 authors who are nationally recognized experts in their respective fields.

Although both of the editors are head and neck surgeons, the emphasis of the book is directed toward the importance of team management of patients with head and neck cancer. To this end, they have enlisted authors who are experts in several allied medical specialities including radiation oncology, neurosurgery, plastic surgery, oral surgery, restorative dentistry, medical oncology, pathology, anesthesia, ophthalmology and nursing.

In spite of the many contributors, there is very little overlap of subject matter. The text comprehensively discusses topics such as nutritional management, pain control, chemotherapy and immunotherapy, nursing care, maxillofacial rehabilitation and dental considerations in such patients. Unfortunately, the book had apparently gone to press before the contribution and impact of the computerized tomographic (CT) scan and myocutaneous flaps had been recognized; they are discussed in only a limited fashion.

This book will be a useful adjunct to any clinician treating patients with head and neck cancer regardless of specialty. Needless to say, it would be an important resource during residency training for head and neck surgeons, radiation therapists and medical oncologists.

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* * *

ANDREWS' DISEASES OF THE SKIN: CLINICAL DERMATOLOGY —Seventh Edition—Anthony N. Domonkos, MD; Harry L. Arnold, Jr, MD, and Richard B. Odom, MD. W.B. Saunders Company, West Washington Square, Philadelphia, PA (19105), 1982. 1,108 pages, 1,277 illustrations, $58.00 U.S., $69.60, Canada.

This is the seventh edition of a textbook that first appeared in 1930, thus continuing a 50-year tradition. A great deal of time and care has been put into this last edition bringing it up to date in all respects. All of the references have been modernized and seem to be selective.

The textbook is not meant to be an exhaustive treatise on all problems in dermatology but more a good reference book for practicing dermatologists and an excellent orientation textbook for residents in dermatology. The book is a reasonable one to suggest to medical students who plan to have a future interest in dermatology although they may not pursue the specialty. It is a very useful book to have on the shelf for referral to general dermatologic problems that one might have in a practice other than dermatology. The sections on therapy are carefully considered and represent the most modern methods of management of dermatologic disease. The photographs are very good although there would have been some advantage to at least a few pages of color photographs which the text does not have.

The *Andrews' Diseases of the Skin* has always been a popular dermatologic textbook and with this excellent revision will continue to be.

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* * *

PROGRESS IN PERINATAL NEUROLOGY—Volume 1—Edited by Rowena Korobkin, MD, Children's Hospital Medical Center, Oakland; and Christian Guilleminault, MD, Stanford Sleep Disorders Clinic and Research Center, Stanford University School of Medicine. Williams & Wilkins, 428 East Preston Street, Baltimore, MD (21202), 1981. 238 pages, $35.00.

The contents of this volume accurately reflect its title; it is an excellent review of the current state of the art in one of the exciting new areas of neurology—neonatal brain disorders. The authors are all experts in their respective fields. They present well-written and succinct reviews of clinical disorders affecting the nervous system in newborn infants, including viral infections, respiratory disorders and anoxia. The chapters on neuroradiology, electroencephalography and evoked responses are particularly well done. Some newer topics are reviewed that are rarely presented in other volumes—for example, infantile hemiplegia and disorders of sucking and swallowing.

Obstetricians, perinatologists, neonatologists and pediatric neurologists will find this book a welcome addition to their library.

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* * *

GENERAL UROLOGY—Tenth Edition—Donald R. Smith, MD, Professor of Urology, Emeritus, University of California, San Francisco, School of Medicine; Visiting Professor of Urology, University of Ain Shams, University of Cairo. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1981. 598 pages, $19.50 (paperback).

It is a pleasure again to review this excellent book on general urology. Donald Smith, distinguished emeritus professor from the University of California, San Francisco, has once again brought his comprehensive and excellent text up to date. He has put a complete view of modern urology into a valuable and useful paperback edition which sells for only $19.50. It is a worthy sequel to the now out-of-print book *The Principles and Practice of Urology*, written by his teacher Dr. Frank Hinman, Sr. I tell students at UCLA that if they know everything in this valuable volume, they will know more than most professors of urology.

One of the best things about this book is that Smith, who presented the first edition in 1957, has continued to enlarge it and update information. The chapters are brought into modern perspective. Particularly appealing is the chapter about kidney transplantation by Oscar Salvatierra. Also a number of important chapters have been assigned to Professor Emil Tanago, Smith's successor as professor at the University of California, San Francisco.

The book should appeal and be particularly useful to medical students and residents who desire a quick, reliable and thorough reference in urology.

WILLARD E. GOODWIN, MD
Professor, Urology Division
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UCLA School of Medicine
Los Angeles

in memoriam

California Medical Association

Crow, Lloyd B., San Francisco. Died August 18, 1982, in Palo Alto, aged 98. Graduate of Northwestern University Medical School, Chicago, 1911. Licensed in California in 1915. Dr. Crow was a member of the San Francisco Medical Society.

Dedinsky, John J., San Jose. Died June 19, 1982, in Saratoga, aged 64. Graduate of the St. Louis University School of Medicine, 1943. Licensed in California in 1952. Dr. Dedinsky was a member of the Santa Clara County Medical Society.

Eldredge, Horace S., Arcadia. Died July 19, 1982, aged 75. Graduate of Northwestern University Medical School, Chicago, 1936. Licensed in California in 1936. Dr. Eldredge was a retired member of the Los Angeles County Medical Association.

Fishback, Dora K., Oakland. Died August 16, 1982, in Berkeley, aged 81. Graduate of Northwestern University Medical School, Chicago, 1936. Licensed in California in 1946. Dr. Fishback was a retired member of the Alameda-Contra Costa Medical Association.

Fleisher, Arthur J., Berkeley. Died July 2, 1982, aged 75. Graduate of University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Fleisher was a retired member of the Alameda-Contra Costa Medical Association.

Khoury, Elias F., Simi Valley. Died July 2, 1982, in Northern California mountains of injuries received in light plane crash, aged 45. Graduate of Loma Linda University School of Medicine, Loma Linda-Los Angeles, 1961. Licensed in California in 1962. Dr. Khoury was a member of the Ventura County Medical Society.

Kiyasu, Kunisada, San Francisco. Died July 23, 1982, in San Francisco, aged 94. Graduate of University of California Medical School, Berkeley-San Francisco, 1921. Licensed in California in 1921. Dr. Kiyasu was a retired member of the San Francisco Medical Society.

Leon, Tim Daniel, Clayton. Died in August 1982, aged 86. Graduate of the University of Nebraska College of Medicine, Omaha, 1932. Licensed in California in 1932. Dr. Leon was a retired member of the Alameda-Contra Costa Medical Association.

Mahon, Edmund J., San Francisco. Died July 6, 1982, in San Rafael, aged 81. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Mahon was a member of the San Francisco Medical Society.

Merchant, Robert F., San Francisco. Died June 23, 1982, in Sacramento, aged 60. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1946. Licensed in California in 1946. Dr. Merchant was a member of the San Francisco Medical Society.

Pendergrass, Clayton I., Clovis. Died July 6, 1982, aged 78. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1930. Licensed in California in 1931. Dr. Pendergrass was a retired member of the Fresno-Madera Medical Society.

Pinder, Donald E., Downey. Died July 2, 1982, in Downey of injuries received in traffic accident, aged 64. Graduate of the Philadelphia College of Osteopathy, 1945. Licensed in California in 1946. MD degree from California College of Medicine, 1962. Dr. Pinder was a member of the Los Angeles County Medical Association.

Rixford, Emmet L., Jr., San Francisco. Died July 31, 1982, in Tiburon, aged 78. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Rixford was a member of the San Francisco Medical Society.

Stimson, Clement A., Petaluma. Died July 30, 1982, in Petaluma, aged 79. Graduate of University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Stimson was a member of the Sonoma County Medical Association.

West, Francis E., San Diego. Died August 24, 1982, aged 75. Graduate of University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. West was a past president of the California Medical Association and of the San Diego County Medical Society.

Wylie, Edwin J., San Francisco. Died September 2, 1982, in Belvedere, aged 63. Graduate of Harvard Medical School, Boston, 1943. Licensed in California in 1943. Dr. Wylie was a member of the San Francisco Medical Society.

Young, Henry Marcus, Ramona. Died August 5, 1982, aged 76. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1935. Dr. Young was a member of the San Diego County Medical Society.

Idaho Medical Association

Bond, S. Wallace, Twin Falls. Died March 4, 1982, aged 85. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1923. Licensed in Idaho in 1938. Dr. Bond was a past president of the Idaho Medical Asssociation and a member of the South Central Idaho District Medical Society.

BUDGE, ALFRED H., Boise. Died February 19, 1982, aged 86. Graduate of Northwestern University Medical School, Chicago, 1922. Licensed in Idaho in 1922. Dr. Budge was a member of the Ada County Medical Society.

DAVIS, GEORGE E., New Plymouth. Died in 1982, aged 75. Graduate of the University of Oregon Medical School, Portland, 1932. Licensed in Idaho in 1935. Dr. Davis was a member of the Southwestern Idaho District Medical Society.

FLORENTZ, THEODORE R., Boise. Died February 5, 1982, aged 72. Graduate of Wayne State University School of Medicine, Detroit, 1941. Licensed in Idaho in 1948. Dr. Florentz was a member of the Ada County Medical Society.

HAHN, ROBERT F., Idaho Falls. Died August 13, 1982, in Idaho Falls of cancer, aged 53. Graduate of St. Louis University School of Medicine, 1953. Licensed in Idaho in 1964. Dr. Hahn was a member of the Idaho Falls Medical Society.

JENSEN, ROBERT H., Caldwell. Died April 9, 1982, aged 55. Graduate of the University of Oregon Medical School, Portland, 1960. Licensed in Idaho in 1962. Dr. Jensen was a member of the Southwestern Idaho District Medical Society.

JOHNSON, HOWARD E., Boise. Died January 21, 1982, aged 50. Graduate of the University of Oregon Medical School, Portland, 1961. Licensed in Idaho in 1969. Dr. Johnson was a member of the Ada County Medical Society.

MACK, JAMES F., Boise. Died December 6, 1981, aged 45. Graduate of St. Louis University School of Medicine, 1962. Licensed in Idaho in 1978. Dr. Mack was a member of the Ada County Medical Society.

MORRIS, JUDSON B., Boise. Died January 1, 1982, aged 71. Graduate of the University of Michigan Medical School, Ann Arbor, 1936. Licensed in Idaho in 1946. Dr. Morris was a member of the Ada County Medical Society.

MOSELEY, H. DON, Coeur d'Alene. Died in 1982, aged 65. Graduate of the University of Tennessee Center for the Health Sciences, Memphis, 1943. Licensed in Idaho in 1947. Dr. Moseley was a member of the Kootenai-Benewah District Medical Society.

New Mexico Medical Society

MCCRORY, JAMES L., Santa Fe. Died June 29, 1982, aged 76. Graduate of Baylor University College of Medicine, Houston, 1938. Licensed in New Mexico in 1947. Dr. McCrory was a member of the Santa Fe County Medical Society.

Utah State Medical Association

PRESTWICH, JAMES SHELDON, Cedar City. Died June 26, 1982, in Cedar City, aged 79. Graduate of the University of Cincinnati College of Medicine, Cincinnati, 1927. Licensed in Utah in 1928. Dr. Prestwich was a member of the Iron County Medical Society.

WRIGHT, JOHN K., Price. June 19, 1982, in Price, aged 61. Graduate of St. Louis University School of Medicine, 1945. Licensed in Utah in 1954. Dr. Wright was a member of the Carbon County Medical Society.

Washington State Medical Association

HEILBRUNN, GERT, Seattle. Died May 8, 1982, aged 71. Graduate of Medizinische Fakultät der Universität, Bern, Switzerland, 1935. Licensed in Washington in 1947. Dr. Heilbrunn was a member of the King County Medical Society.

WATERMAN, JOHN H., Eastsound. Died in May 1982, aged 76. Graduate of the University of Nebraska College of Medicine, Omaha, 1933. Licensed in Washington in 1981. Dr. Waterman was a member of the Skagit Island County Medical Society.

YARBRO, JESSE L., Seattle. Died April 11, 1982, aged 67. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1948. Licensed in Washington in 1950. Dr. Yarbro was a member of the King County Medical Society.

Wyoming Medical Society

HAMBLY, ALVIN S., Cheyenne. Died July 17, 1982, in Cheyenne, aged 57. Graduate of University of California Medical School, Berkeley-San Francisco, 1948. Licensed in Wyoming in 1976. Dr. Hambly was a member of the Laramie County Medical Society.

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(Continued from Page 16)

January 12—**12th Annual Gastroenterology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375

January 12—**22nd Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday. 4½ hrs. $75. Contact: Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 12—**Office Urology.** LLU. Wednesday 4 hrs.

January 14-15—**Third Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Bernard L. Tucker, MD, 1136 W. 6th St., Los Angeles 90017. (213) 482-3121.

January 14-15—**10th Annual Santa Clara County Surgical Seminar—Critical Care and Current Concepts.** Santa Clara Co. Surgical Seminar Assn. at Le Baron Hotel, San Jose. Friday-Saturday. 15 hrs. $160. Contact: Surgical Seminar, c/o Kenneth Watanabe, MD, 150 N. Jackson Ave., #209, San Jose 95116.

January 16-18—**International Symposium: The Psychobiology of Alcoholism.** UCLA at Beverly Hills. Sunday-Tuesday.

January 17-19—**Society of Thoracic Surgeons.** Hilton, San Francisco. Monday-Wednesday. Contact: STS, 111 E. Wacker Dr., Chicago 60601.

January 17-21—**Postgraduate Institute for Emergency Physicians—Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs. $425.

January 17-21—**Advanced Microbiology: Recent Developments and New Frontiers.** American Society of Clinical Pathologists at San Francisco. Monday-Friday. 32 hrs. $600/$700. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

January 17-21—**Interventional Radiology and Diagnostic Imaging Modalities.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $400.

January 20-22—**5th Annual Postgraduate Course on Surgery.** UCD at Holiday Inn, Sacramento. Thursday-Saturday. 15 hrs.

January 22-29—**Advanced Problems in Cardiac Emergencies.** UCSD, American Inst. of Postgraduate Education, Scripps Memorial Hospital at Kona Surf Hotel, Kona, Hawaii. One week. 21 hrs. $325. Contact: AIPE, P.O. Box 2101, Del Mar 92014. (714) 454-3212.

January 22-30—**11th Annual Diagnostic Radiology Seminars.** UCSF at Waiohai Hotel, Kauai, Hawaii. One week. 31 hrs. $350.

January 24-26—**Midwinter Clinical Conference in Ophthalmology and Otolaryngology.** Research Study Club of Los Angeles at Hilton, Los Angeles. Monday-Wednesday. 21 hrs. $200. Contact: Research Study Club, P.O. Box 49412, Los Angeles 90049.

January 24-28—**Primary Care: Current Management of Common Office Problems.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Tuesday. 33 hrs.

January 26—**Biannual Stroke Symposium.** American Heart Assn., Santa Clara Co. Chap., at Le Baron Hotel, San Jose. Wednesday. Contact: Harriet M. Schutte, RN, PhD, AHA, 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

January 29—**Practical Use of the Visual Physiology Laboratory.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $50. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

January 29—**Ovulation Update: 1983.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. $75. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

January 29-February 4—**9th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Saturday-Friday. 25 hrs.

January 31-February 3—**8th Annual Winter Ski and Study Symposium.** Calif. Chaps. 1 and 2, American Academy of Pediatrics, at Caesar's, Lake Tahoe. Monday-Thursday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 31-February 4—**Topics in Emergency Medicine.** UCSF. Monday-Friday. 35 hrs. $350.

February 2-4—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 23 hrs. Contact: Edith S. Bookstein, 7810 Lookout Dr., La Jolla 92037. (714) 454-3212.

February 2-4—**5th Annual Immunoassay Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 21 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 2-4—**10th Annual Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 23 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

February 3-6—**Cognitive, Emotional and Neurophysiologic Effects of Head Trauma: Post-Concussion Syndrome.** So. Calif. Neuropsychiatric Institute at La Quinta Hotel, La Quinta. Thursday-Sunday. 15 hrs. Contact: Gail Waldron, MD, Prog. Dir., SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

February 4-6—**21st Clinical Conference in Pediatric Anesthesiology.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $175. Contact: Wayne Herbert, MD, Childrens Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 669-2262.

February 4-6—**Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 4-6—**35th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. $125, members; $175, nonmembers. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 5-11—**Perinatal Medicine.** USC at Royal Lahaina, Maui. One week. 23 hrs. $425.

February 6-10—**Lake Tahoe Vitreo-Retinal Symposium.** Retina Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

February 6-11—**OB/GYN Update.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 22 hrs.

February 6-12—**Los Angeles Radiological Society—Annual Post Convention Seminar.** Hyatt Regency, Kaanapau, Maui. One week. 20 hrs. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 7-11—**Nutritional Aspects of Obesity Management.** American Society of Bariatric Physicians at Kauai Surf, Kauai, Hawaii. Monday-Friday. 20 hrs. $295, members; $325, nonmembers. Contact: ASBP, 5200 S. Quebec, Suite 300, Englewood, CO 80111. (303) 779-4833.

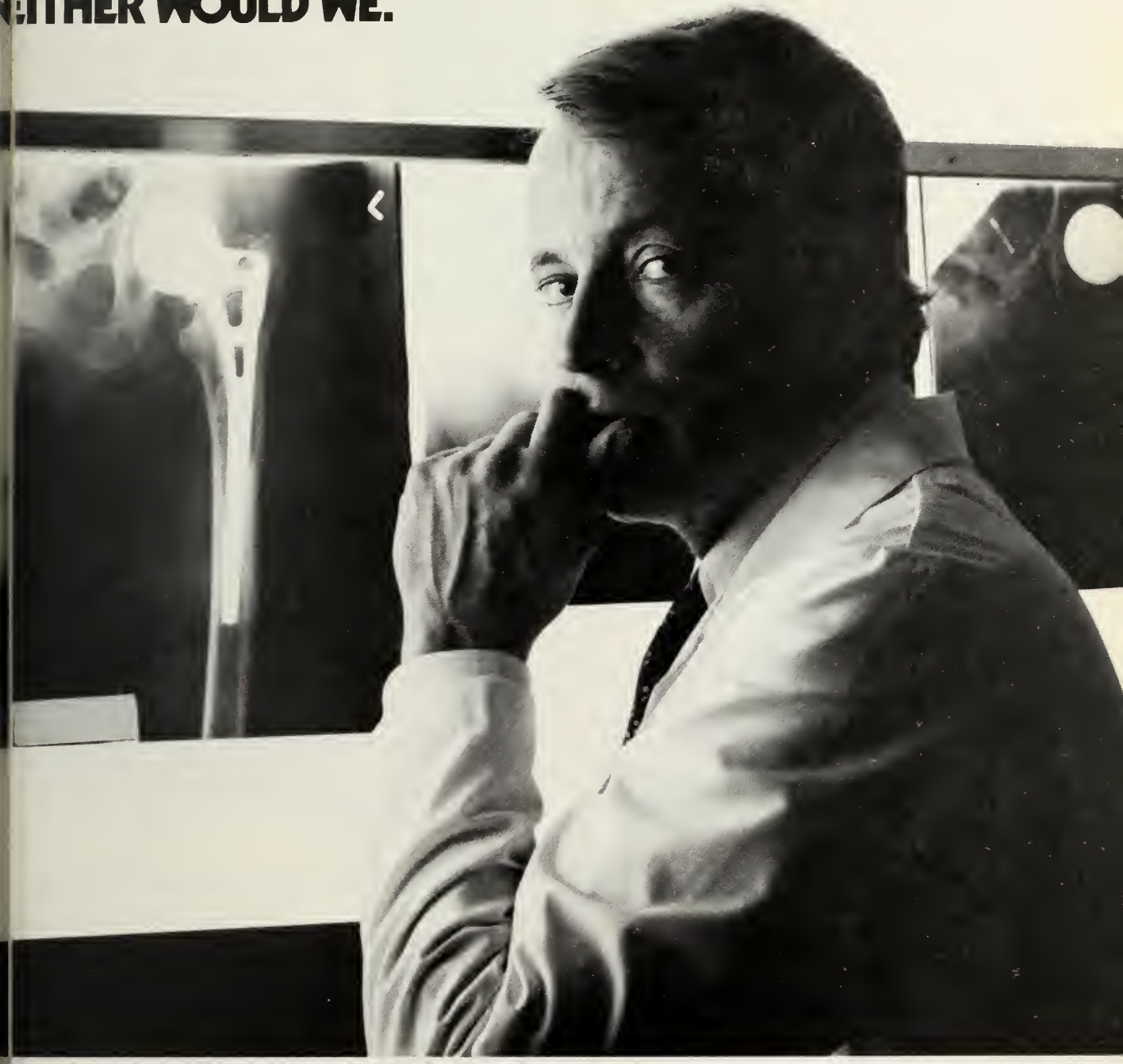
February 7-12—**Family Practice Refresher Course.** UCI at Marriott, Newport Beach. Monday-Saturday. 50-56 hrs. Contact: UCI Extension, P.O. Box AZ, Irvine 92714. (714) 833-5414.

February 9—**Cardiology Symposium on Pacemakers.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

(Continued on Page 44)

OULD YOU GUARANTEE THERE WON'T BE PROBLEMS VER THE NEXT 5 YEARS?

EITHER WOULD WE.



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AN INTERINSURANCE EXCHANGE
OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

(Continued from Page 42)

February 9—**Common Skin Diseases.** LLU. Wednesday.

February 9-11—**Recent Advances in Neurology.** UCSF at Fairmont, San Francisco. Wednesday-Friday.

February 10-12—**Practical Cardiology for Family Physicians, 1983.** American College of Cardiology at Eisenhower Medical Center, Rancho Mirage. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

February 11—**Geriatric Medicine, Symposium II—"Special Health Concerns of the Elderly."** Sutter Community Hospitals at Red Lion Inn, Sacramento. Friday. 7 hrs. Contact: Marsha Vacca, Geriatrics Coordinator, Sutter Gen. Hosp., 28 and L Sts., Sacramento 95816. (916) 454-2222, ext. 1233.

February 13-18—**11th Obstetric Anesthesia Conference.** Ohio State Univ. at Maui Surf Hotel, Maui, and Sheraton Waikiki, Oahu. Sunday-Friday. 25 hrs. Contact: Ohio State Univ. Hospitals, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, OH 43210. (614) 421-8487.

February 14-18—**38th Annual Postgraduate Assembly.** OB-GYN Assembly of So. Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

February 14-18—**Current Methods in Blood Banking and Immunohematology.** American Society of Clinical Pathologists at San Diego. Monday-Friday. 31½ hrs. $560/$660. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 14-25—**Intensive Residency in Occupational Medicine, II.** UCSF at Golden Gateway Holiday Inn, San Francisco. Two weeks. 80 hr.

February 15-18—**Clinical Hematology and Oncology: 1983.** Scripps Clinic and Research Foundation at Sheraton Harbor Island, San Diego. Tuesday-Friday. 31 hrs. $390. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 17-19—**Therapeutic and Diagnostic Uses of the Cardiac Catheter.** American College of Cardiology at Bonaventure Hotel, Los Angeles. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

February 17-19—**Pediatric Urology.** American Urological Assn. at Hilton, San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Education, AUA, P.O. Box 25147, Houston, TX 77265. (713) 790-6070.

February 20-24—**Winter Sports Injuries.** UCD at Hyatt, Lake Tahoe. Sunday-Thursday. 15 hrs.

February 21-23—**Update on Bone and Calcium.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF. Monday-Wednesday.

February 21-25—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $365.

February 23-24—**Neurological Problems.** UCLA and Federation of Western Neurological Societies at UCLA. Wednesday-Thursday.

February 23-25—**New Imaging Modalities in Radiology.** Memorial Hospital Medical Center of Long Beach at Hilton Riviera, Palm Springs. Wednesday-Friday. 18 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

February 23-March 1—**Adolescent/Young Adult Medicine.** Hurley Medical Center at Wailea Beach Hotel, Maui. One week. 20 hrs. Contact: Hurley Med. Ctr., Dept. of Cont. Med. Ed., One Hurley Plaza, Flint, MI 48504. (313) 766-0142.

February 25-26—**Ophthalmology Update on Basic Sciences for the Clinician.** UCD, PMC, UCSF, STAN at San Franciscan Hotel, San Francisco. Friday-Saturday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2763.

February 26-27—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 11 hrs. $250.

February 26-27—**Basic Neuroscience.** STAN. Saturday-Sunday. 11 hrs. $250.

February 26-27—**Immunology.** STAN. Saturday-Sunday. 11 hrs. $250.

February 26-27—**Mechanisms of Drug Action.** STAN. Saturday-Sunday. 11 hrs. $250.

February 27-March 2—**Basic Cardiology.** UCSF at South Lake Tahoe. Sunday-Wednesday.

ALASKA

November 19-20—**Gastroenterology Conference.** Anchorage. Friday-Saturday. Providence Hospital. 14 hours Category 1 credit. Fee: $65. For further information, fees, credit and program contact: Judy Kyle, Education and Training Department, Providence Hospital, 3200 Providence Drive—Pouch 6604, Anchorage, AK 99502. (907) 276-4511, Ext. 1005.

IDAHO

See Washington Listings: February 5-12, 12-19, 14-18, 19-26, 26-March 5, 5-12.

MONTANA

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 14-16—**The 12-Lead ECG for the Primary Care Physician.** Albuquerque. Thursday-Saturday. Presbyterian Hospital. 23 credit hours, also AAFP Prescribed. Contact: NM Heart Institute, 2403 San Mateo NE, Albuquerque, NM 87108. (505) 884-3717.

(Continued on Page 56)

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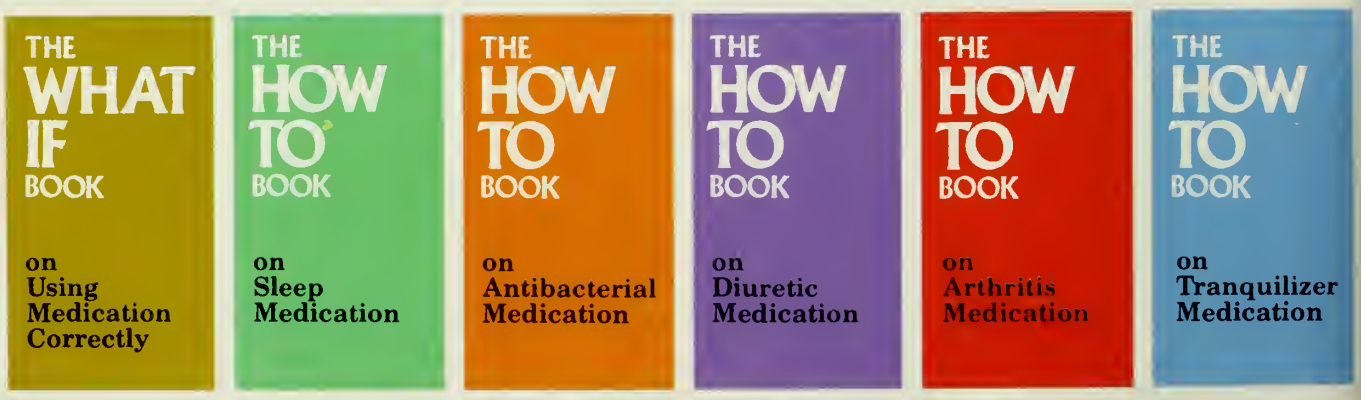

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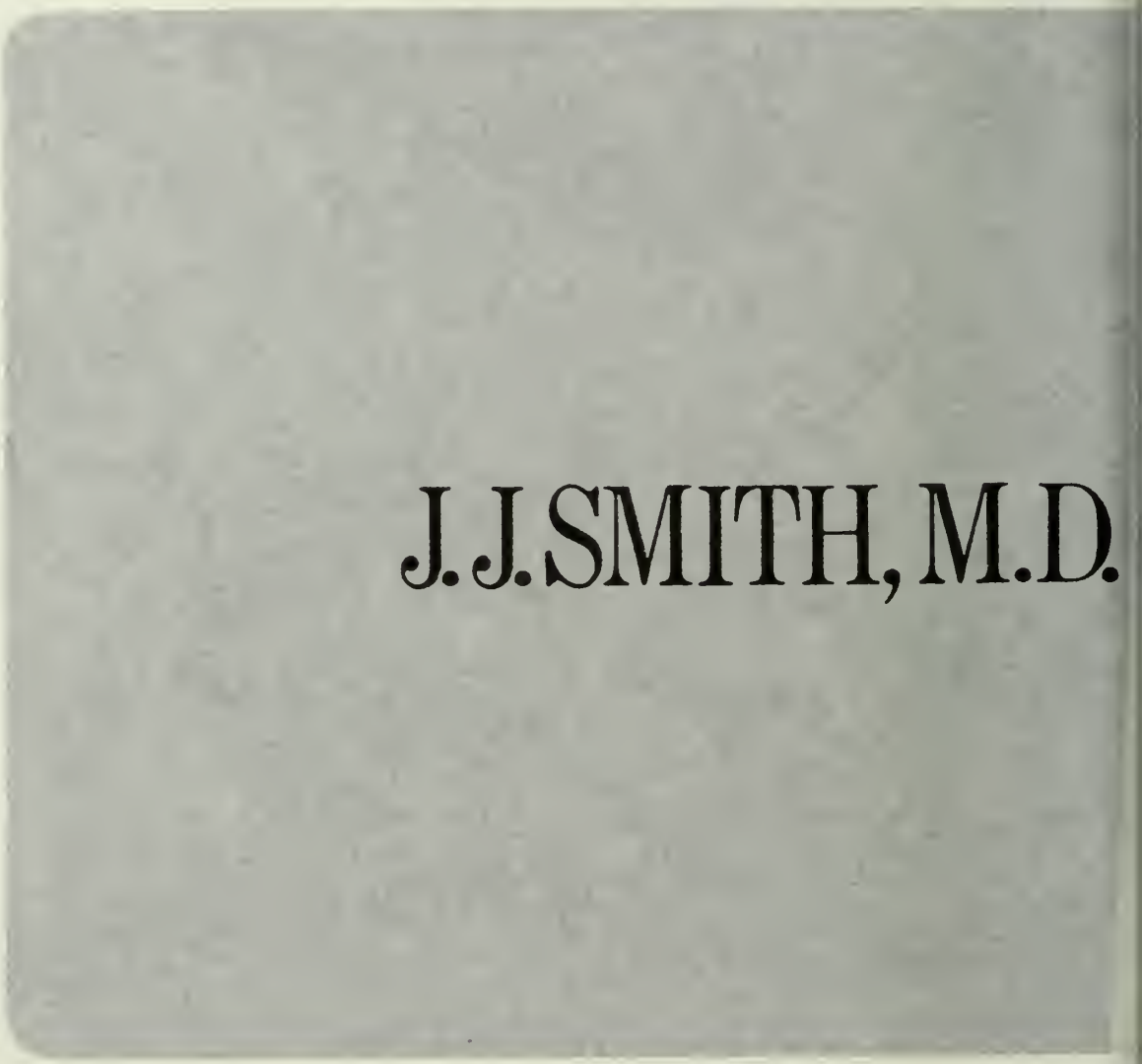


*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her moderate to severe sweats and hot flushes. Relieves her discomfort. PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CA

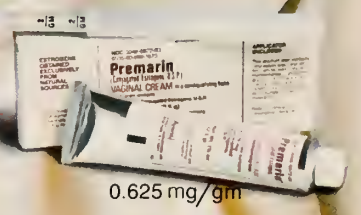
IT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/gm

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis.

Please see following page for Brief Summary of Prescribing Information.

PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING)
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions. 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembo or during periods of prolonged immobilization. Estrogens should not be used in persons active thrombophlebitis, thromboembolic disorders, or in persons with a history of disorders in association with estrogen use. They should be used with caution in patients cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per comparable to those used to treat cancer of the prostate and breast have been shown to inc the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. doses of this size are used, any of the thromboembolic and thrombotic adverse effects shou considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pai tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has reported in women taking estrogen-containing oral contraceptives. Increased blood pre may occur with use of estrogens in the menopause and blood pressure should be monitore estrogen use. A worsening of glucose tolerance has been observed in patients on estro containing oral contraceptives. For this reason, diabetic patients should be carefully obse Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone m tases.

PRECAUTIONS: Physical examination and a complete medical and family history shou taken prior to the initiation of any estrogen therapy with special reference to blood pres breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a ge rule, estrogen should not be prescribed for longer than one year without another ph examination being performed. Conditions influenced by fluid retention such as ast epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. C patients may develop manifestations of excessive estrogenic stimulation, such as abnorr excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated w increased incidence of mental depression. Patients with a history of depression shou carefully observed. Preexisting uterine leiomyomata may increase in size during estroge The pathologist should be advised of estrogen therapy when relevant specimens are subm If jaundice develops in any patient receiving estrogen, the medication should be discont while the cause is investigated. Estrogens should be used with care in patients with impaire function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3; incr norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total t hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin u is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, includin contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmeno premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of u fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of ce secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); na vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma whic persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorr eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to co lenses; headache, migraine, dizziness, mental depression, chorea, increase or decrea weight, reduced carbohydrate tolerance; aggravation of porphyria, edema, changes in lib

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in femal

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe vaso symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1. or more daily).
The lowest dose that will control symptoms should be chosen and medication sho discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month inte
2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian fa Osteoporosis.
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3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg eve hours for five doses, or 1.25 mg every four hours for five days.
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Inoperable progressing breast cancer in appropriately selected men and postmenop women—10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cance appropriate measures taken to rule out malignancy in the event of persistent or rec abnormal vaginal bleeding.

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(Continued on Page 54)

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(Continued from Page 44)

October 15—**Gynecologic Cancer 1982.** Los Alamos. Friday. Los Alamos Medical Center. 6 credit hours. Contact: James M. Cooper, MD, Los Alamos Council on Cancer, Los Alamos, NM 87544. (505) 662-4412.

November 5—**Current Issues in Cancer Rehabilitation.** Albuquerque. Friday. Hilton Inn. 7 credit hours. Contact: Paul Duncan, MD, 500 Walter NE, #409, Albuquerque, NM 87102. (505) 247-0216.

November 5-6—**Hypnosis in Clinical Medicine: Applications for Everyday Practice.** Albuquerque. Friday-Saturday. Sheraton Old Town. 14 credit hours, also AAFP Prescribed. Contact: UNM School of Medicine, Office of CME, Albuquerque, NM 87131. (505) 277-3942.

November 5-6—**Symposium on Critical Care.** Farmington. Friday-Saturday. The Inn. 12 credit hours, also AAFP Prescribed. Contact: San Juan County Medical Society, 814 West Maple Street, Farmington, NM 87401. (505) 325-5011.

November 12-13—**New Mexico Medical Society Interim Meeting.** Las Vegas, New Mexico. Friday-Saturday. Highlands University. 7 credit hours, also AAFP Prescribed. Contact: NM Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

February 14-17—**Taos Medical Symposium.** Taos. Monday-Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II, MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

February 28-March 4—**Purgatory Ski Symposium.** Durango, Colorado. Monday-Friday. Tamaron Lodge. 20 credit hours, also AAFP. Contact: Gwenn Robinson,MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

OBSTETRICS AND GYNECOLOGY

October 21-23—**Pacific Northwest Review of Obstetrics and Gynecology.** Portland. Thursday-Saturday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

October 29-31—**Salishan Conference: Cardiology.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: OHSU-CME.

(Continued on Page 58)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

The Research Study Club

PRESENTS

52ND ANNIVERSARY

MID-WINTER CLINICAL CONFERENCE IN

OPHTHALMOLOGY

JANUARY 23, 24, 25, 26, 1983 • HILTON HOTEL, LOS ANGELES

• GLAUCOMA UPDATE • LASERS • COMPUTORS IN OPHTHALMOLOGY
• NEURO-OPHTHALMOLOGY • SPECIAL WORKSHOPS

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Associate Professor of Pathology
Johns Hopkins Hospital, Baltimore, Maryland

J. RIGBY SLIGHT, MD
Associate Clinical Professor of Ophthalmology
Director of the Glaucoma Service
University of California, San Diego, California

JONATHAN HERSCHLER, MD
Associate Professor and Head of
Department of Ophthalmology
University of Arizona, Medical School
Tucson, Arizona

E. MICHAEL VAN BUSKIRK, MD
Associate Professor of Ophthalmology
Oregon Health Sciences University
Portland, Oregon

H. DUNBAR HOSKINS, MD
Associate Clinical Professor
University of California Medical School
San Francisco, California

BRIAN YOUNGE, MD
Associate Professor of Ophthalmology and
Consultant in Ophthalmology and Neurology
The Mayo Clinic, Rochester, Minnesota

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FEE: Practicing physicians—$100 if attending Mid-Winter Course; $150 if not attending Course
Residents—$75 if attending Course; $100 if not attending Course

---

Registration Deadline—January 1, 1983

Registration Fee: $225 Practicing Physicians ($200 if received before 12/15/82); $100 Resident Physicians

For Additional Information: Research Study Club, P. O. Box 49412, Los Angeles, California 90049

(Category I Credit 24 hours, CMA, AMA)

(Continued from Page 56)

November 4-5—**Sommer Lectures—Oregon Medical Association Annual Meeting.** Portland. Thursday-Friday. Thunderbird Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Friday—7:30-8:30 a.m. Contact: Thomas Schwenk, MD, (801) 350-4111.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

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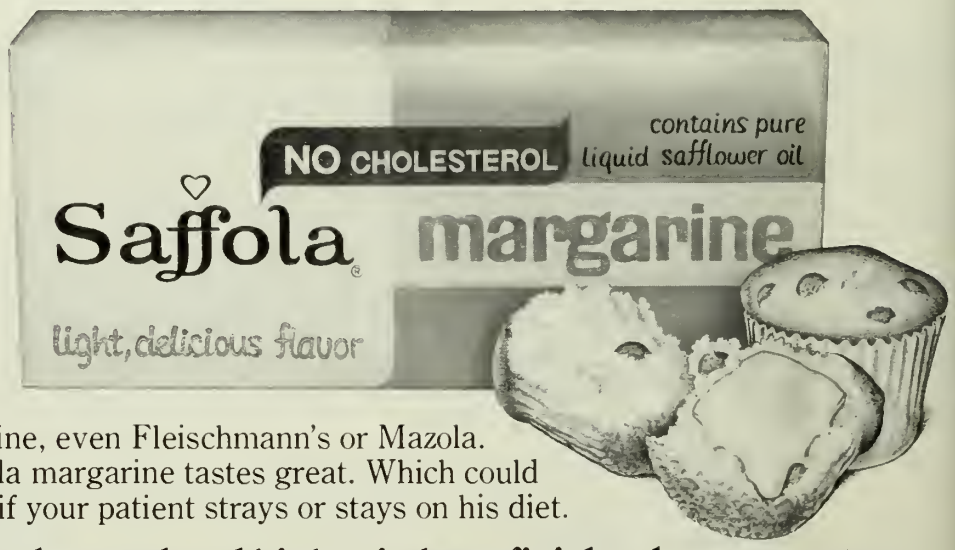

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Jtah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

November 5—**Genetic Epidemiology of Cancer in Utah Mormons/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

November 12-13—**New Techniques in Pulmonary Medicine** (Sponsors: LDS Hospital/University of Utah). Salt Lake City. Friday-Saturday. Little America. 10 hrs. $70. Contact: C. Duane Schmidt, MD (801) 353-8201.

November 19—**Common Nerve Entrapments** (Sponsor: McKay-Dee Hospital Center). Ogden. Friday. 1 hr. No fee. Contact: (801) 627-3202.

December 3—**Applications of Mass Spectrometry to Quantitative and Structural Analysis in Biochemistry/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

January 7—**Effect of Surgery for Variceal Hemorrhage on Hepatic Blood Flow and Cerebral Function/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

January 21—**Treatment of Upper Extremity Pain Syndromes** (Sponsor: McKay-Dee Hospital Center). Ogden. Friday. 1 hr. No fee. Contact: (801) 627-3202.

January 21-23—**7th Annual U of U Seminar on Sexual Function/Dysfunction** (Sponsor: University of Utah). Park City. Friday-Sunday. 19 hrs. Fee: $200. Contact: Claire Turner (801) 581-5809.

January 26-February 3—**Air Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. Credit and fee to be announced. Contact: Dennis C. Brimhall, MD (801) 581-2682.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION as required by the Act of August 12, 1970; Section 3685, Title 39, United States Code, for THE WESTERN JOURNAL OF MEDICINE, published monthly at San Francisco, California, for September, 1982.

1. Location of known office of publication: 731 Market Street, San Francisco, California 94103.

2. Location of the headquarters or general business office of the publisher: 731 Market Street, San Francisco, California 94103.

3. Publisher: California Medical Association, 731 Market Street, San Francisco; Editor, Malcolm S. M. Watts, M.D., 731 Market Street, San Francisco; Managing Editor, David Greer, 731 Market Street, San Francisco.

4. Owner: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given.) California Medical Association, 731 Market Street, San Francisco, California (an unincorporated association).

5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.

6. Paragraphs 4 and 5 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting, also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner. Names and addresses of individuals who are stockholders of a corporation which itself is a stockholder or holder of bonds, mortgages or other securities of the publishing corporation have been included in paragraphs 4 and 5 when the interests of such individuals are equivalent to 1 percent or more of the total amount of the stock or securities of the publishing corporation.

7. Average number of copies each issue during preceding 12 months: Total 46,158, paid circulation by mail subscription, 44,864; sales through dealers and carriers, street vendors and counter sales, 0; free distribution (including samples) by mail, carrier or other means, 571; total distribution, 44,602; office use, leftover, unaccounted, spoiled after printing, 772; total net press run, 46,158. Single issue nearest to filing date, September, 1982: Total 45,900; paid circulation by mail subscription, 44,803; sales through dealers and carriers, 0; free distribution (including samples) by mail, carrier or other means, 517; total distribution, 45,320; office use, leftover, unaccounted, spoiled after printing, 580; total net press run, 45,900. David Greer, Managing Editor.

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January 31-February 4—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. $350. Contact: John Matsen, MD (801) 581-5514.

February 4—**Host Functions Essential for Bacteriophage Growth/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

February 14-17—**12th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 28 hrs. $280. Contact: Linda Twitchell (801) 581-8633.

February 18-22—**28th Annual Postgraduate Course in Anesthesiology** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hilton Hotel. 17 hrs. Fee to be announced. Contact: Ted Stanley, MD (801) 581-7647.

February 19-22—**24th Annual Ob/GYN Postgrad Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 23-26—**Perinatal Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 25—**Special Problems in Stroke Recovery** (Sponsor: McKay-Dee Hospital Center). Ogden. Thursday. 1 hr. No fee. Contact: (801) 627-3202.

March 4—**Blood and Marrow Neutrophil Kinetics During Group B Streptococcal Sepsis/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

April 1—**Connective Tissue Genes: Their Structure and Expression in Cells of the Arterial Wall/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

April 5-8—**The 5th Annual RMCOEH Occupational and Environmental Health Conference: Reproduction: The New Frontier in Occupational and Environmental Health Research** (Sponsor: University of Utah/RMCOEH). Park City. Tuesday-Friday. Prospector Square. Credit and fee to be announced. Contact: Ms. K. Blosch (801) 581-5710.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

October 15-16—**The Insulin Pump in Clinical Practice.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

October 20—**Advances in Thyroid Disease.** Seattle. Wednesday. Northwest Hospital. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500 ext. 1737.

October 20-22—**Advances in Internal Medicine.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

October 21-22—**Nosocomial Infections and Herpes/Hepatitis.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

October 22—**Gynecologic Surgery.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

October 22-23—**Care and Rehabilitation of the Injured Wrist.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

October 28-29—**Office Gynecology for Primary Physicians.** Seattle. Thursday-Friday. Park Hilton. Contact: U/W.

November 4-5—**Current Concepts in Drug Therapy.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 5—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

November 5-6—**Outpatient Surgical Care.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

November 11-12—**Topics in Emergency Medicine.** Seattle. Thursday-Friday. Sea-Tac Marriott Hotel. Contact: Heidi Hilby, Executive Secretary, Washington Chapter, American College of Emergency Physicians, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

November 11-12—**Renal Symposia.** Seattle. Thursday-Friday. Park Hilton Hotel. Contact: Marilyn R. Carlson, Continuing Education, 1551 North 115th, Seattle, WA 98133. (206) 364-0500 ext. 1737.

November 12—**Eye Care in General Practice.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 12-13—**Diabetes.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

November 13—**Medicine and Religion.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

November 18-19—**Psychiatric Emergencies.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

November 19—**Neuroophthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

November 19-20—**(ALASKA) Gastroenterology Conference.** Anchorage, Alaska. Friday-Saturday. Providence Hospital. 14 hours Category 1 credit. Fee: $65. Contact: Judy Kyle. Education and Training Department, Providence Hospital, Pouch 6604, Anchorage, AK 99502. (907) 276-4511 ext. 1005.

November 20-27—**(HAWAII) 3 For 1: Proctology, Psychiatry, Principles.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

November 20-27—**(HAWAII) Financial Planning.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

December 2-3—**Surgical Aspects of Lung Disease.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

(Continued on Page 63)

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

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(Continued from Page 61)

December 3—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 4—**Orthopaedics for Attorneys.** Seattle. Saturday. Sheraton Hotel: Contact: U/W.

December 6-7—**American College of Physicians MKSAP IV.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

December 9-10—**Aging and Elderly.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: U/W.

January 13-14—**Sex and the Family.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

January 20-21—**Cytology.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

January 21-22—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 21-23—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 23—**Dyslexia.** Seattle. Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 27-28—**Beta Blockers and Calcium Antagonists.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

January 29-30—**Benefits and Problems of Exercise.** Seattle. Saturday-Sunday. Swedish Hospital. Contact: U/W.

February 3-4—**Ultrasound/Echocardiography.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 4-5—**Diseases of the Elderly.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 5-12—**(IDAHO) Management of Pain.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 12-19—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 14-18—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Friday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 17-18—**Soft Tissue Surgery.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 19-26—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Contact: U/W.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-March 5—**(IDAHO) Sports Medicine 83.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 4-5—**High-Risk Infants of the 1980s.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

March 5-12—**(IDAHO) Management of Obesity.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 10-11—**Nutrition and Bone Metabolism.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

March 12-19—**(HAWAII) Office Gynecology.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

March 16-18—**MKSAP: Medical Knowledge Self-Assessment Program.** Seattle. Wednesday-Friday Virginia Mason Medical Center. Contact: VMMC.

March 18—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

March 18-19—**Recent Developments in Occupational Medicine.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 19-26—**(HAWAII) Advances in Family Practice.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 25-26—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 26-April 2—**(HAWAII) Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Pathology Day.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

April 1-2—**Compensation Law/Public Policy/Back Pain.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 8-9—**Management of Obesity. Seattle.** Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 11-22—**Rehabilitation Medicine Review.** Seattle. Sunday-Thursday. Sheraton. Contact: U/W.

April 14-15—**Vascular Disease/Primary MDs.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

April 22-24—**Office Laboratory Diagnosis for the Clinician.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

April 28-29—**Financial Planning for Physicians.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

May 6-7—**Advances in Behavioral Medicine.** Seattle. Thursday-Friday. Swedish Hospital. Contact: U/W.

May 13—**Medical Alumni Day.** Seattle. Thursday. U/W Health Sciences Building. Contact: U/W.

May 13-14—**Hypertension.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 14—**Sexually Transmitted Diseases in Homosexual Men.** Seattle. Friday. Swedish Hospital. Contact: U/W.

May 19-21—**Office Management of Joint Disease.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

May 20-21—**Prescription and Nonprescription Drugs.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 26-27—**Benefits/Problems of Exercise in Women.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

May 26-27—**Clinical Neurogenetics.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

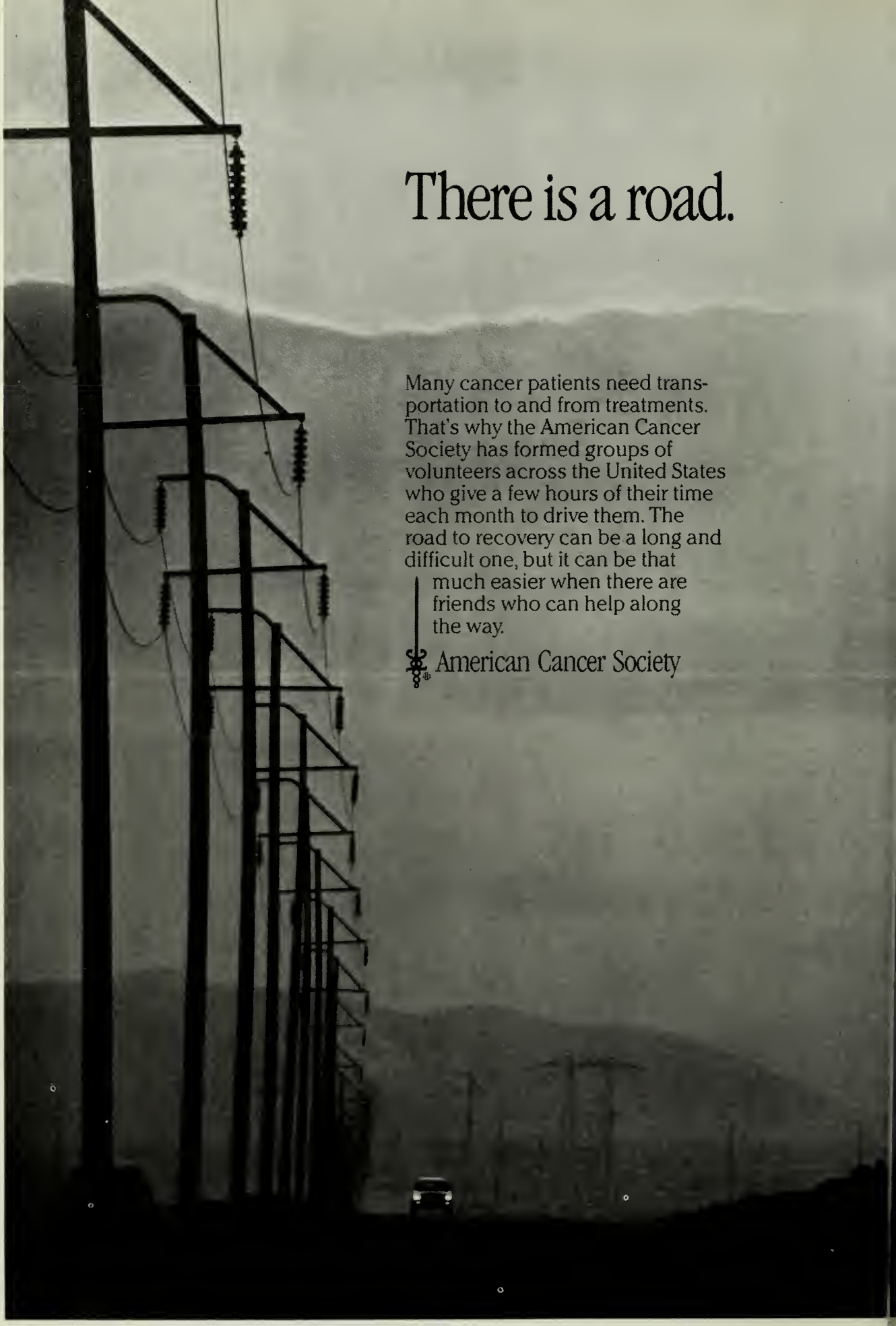
June 2-3—**Managerial Skills.** Seattle. Wednesday-Thursday. Children's Orthopedic Hospital. Contact: U/W.

June 3—**Endocrine Day.** Seattle. Friday. U/W Health Sciences Building. Contact: U/W.

June 3-4—**Acute Medical Problems.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

June 9-11—**Common Office Procedures.** Seattle. Wednesday-Friday. U/W Health Sciences Building. Contact: U/W.

(Continued on Page 66)



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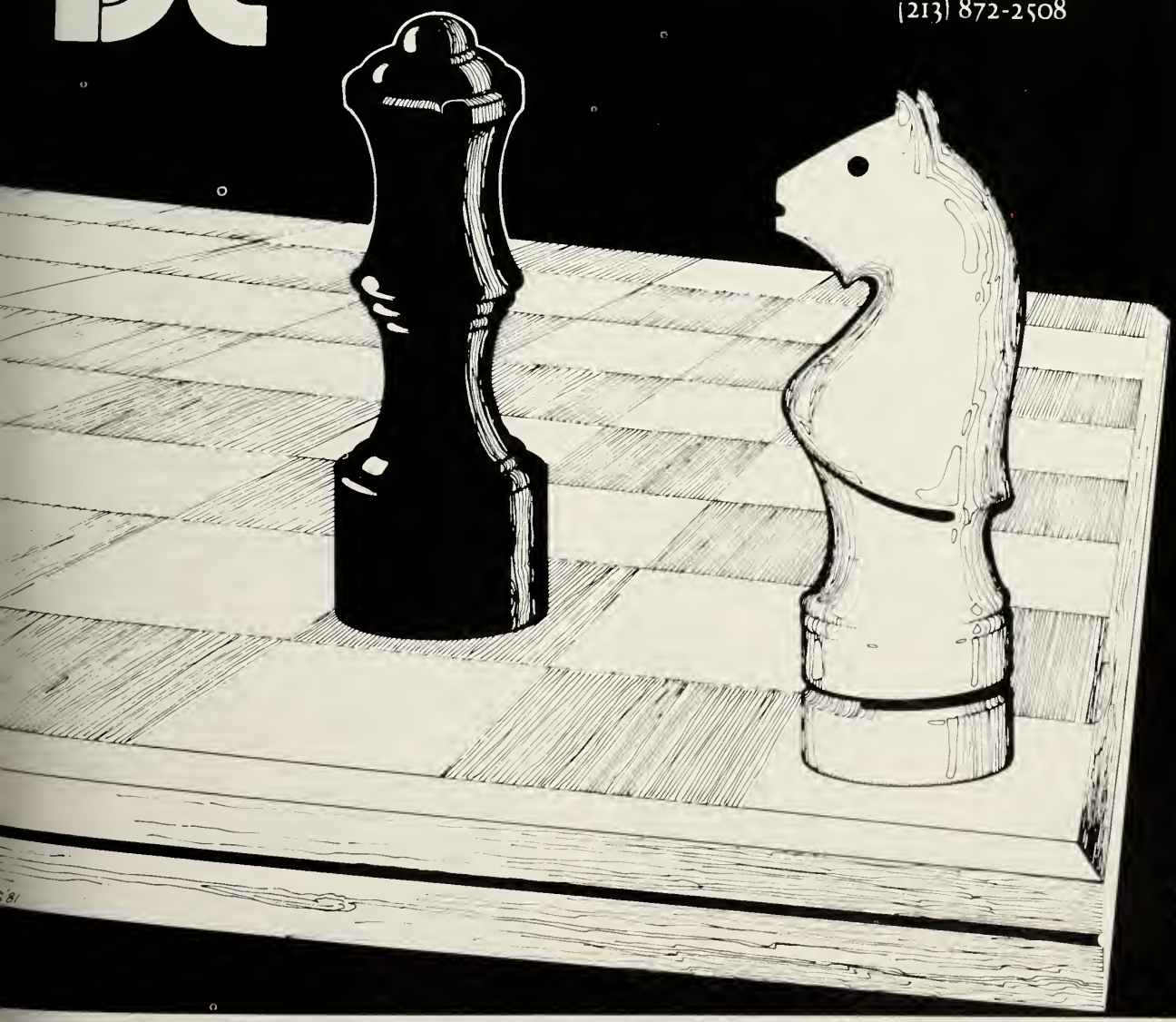


WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: 1983—date and place to be announced.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: May 19-21, 1983, Doubletree Inn, Tucson.

California Medical Association—731 Market St., San Francisco 94103. (415) 777-2000. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. (303) 861-1221. Annual Meeting: 1983—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1983: date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1983—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 12-15, 1983. Elko Convention Center, Elko.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 247-0539. Annual Meeting: May 4-6, 1983. Four Seasons Motor Hotel, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1983—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Winter Seminar: January 21-22, 1983, Rawlins; Annual Meeting: June 29-July 2, 1983, Jackson Lake Lodge, Moran.

Continued from Page 63)

June 16-17—**Human Immunogenics.** Seattle. Wednesday-Thursday. Seattle. U/W Health Sciences Building. Contact: U/W.

June 22-24—**Burn.** Seattle. Tuesday-Thursday. Sheraton Hotel. Contact: U/W.

June 23-24—**Nosocomial Infections Herpes Hepatitis.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

June 27-29—**(OREGON) Office Management of Common Psychiatry Problems.** Sun River. Sunday-Tuesday. Sun River Hotel. Contact: U/W.

June 30-July 1—**(OREGON) Arts and Medicine.** Ashland. Wednesday-Thursday. Southern Oregon State College. Contact: U/W.

July 21-22—**American College of Physicians MKSAP VI.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

July 28-30—**Debates in Otolaryngology.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

July 29-31—**Washington State Society of Anesthesiologists: Seafair V Anesthesia Meeting.** Seattle. Sheraton. Contact: Washington State Society of Anesthesiology, Marcia Wahlman, Executive Secretary, 2033 Sixth Avenue, Suite 900, Seattle, WA 98212. (206) 623-4801.

August 4-5—**Sports Medicine Summer 1983.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

August 25-26—**Urology for Urologists.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

WYOMING

January 21-22—**Wyoming Medical Society Winter Seminar.** Rawlins. Friday-Saturday. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

June 29-July 2—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

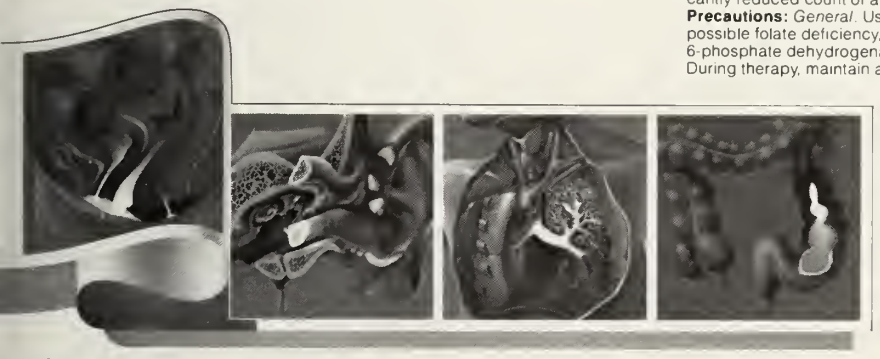
Index to
The Western Journal of Medicine Advertising

AMERICAN CANCER SOCIETY 64
AYERST LABORATORIES
Inderide 28, 29, 30
Premarin Tabs/Vag Cream 47, 48, 49, 50
BANKERS INVESTMENT COMPANY, THE 60
BETH ISRAEL CONFERENCE PROGRAM
1983 Winter Schedule 2
BOOTS PHARMACEUTICALS, INC.
Rufen 23, 24
BOYLE & COMPANY/PHARMACEUTICALS
Citra Forte Syrup-Citra Forte Capsules 13
BURROUGHS WELLCOME CO.
Zyloprim 41
CALIFORNIA MEDICAL ASSOCIATION
112th Annual Session 39
CLASSIFIED 52, 54, 55
COOPERATIVE OF AMERICAN PHYSICIANS, THE
Mutual Protection Trust 62
CPS MEDICAL BILLING 53
DOCTORS' CO., THE 43
ELI LILLY & CO.
Ceclor 3
FAMILY HEALTH PROGRAM 55
HOSPITAL OF THE GOOD SAMARITAN, THE
Controversies in the Management of Early Breast Cancer ... 59
HUMANA/THE HOSPITAL COMPANY 55
INTERNATIONAL CONFERENCES
1983 CME Cruise 26
NORCAL MUTUAL INSURANCE CORPORATION 15
NORTHWEST HOSPITAL
Primary Care Conference 55
PFIZER
Procardia 32, 33, 34, 35, 36, 37, 38
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 31
PRACTICE SERVICE CORPORATION 65
RESEARCH INDUSTRIES INC.
Rimso-50, Rimso-100 5
RESEARCH STUDY CLUB
52nd Anniversary—
Mid-Winter Clinical Conference in Ophthalmology 57
ROCHE LABORATORIES
Bactrim ..... 3rd and 4th covers
Valium ..... 2nd cover, 1, 2
Medication Education 45, 46
SMITH KLINE & FRENCH LABORATORIES
Dyazide 40
E.R. SQUIBB & SONS, INC.
Corgard 8, 9, 10
Velosef 19, 20, 21, 22
STAFF RESOURCES INC. 26
UNIVERSITY OF PITTSBURGH
Course: New Approach to Diseases
Due to Immune Mechanisms 2
UNIVERSITY OF UTAH SCHOOL OF MEDICINE
Snowbird Conferences 55
UPJOHN CO., THE
Motrin 27
WESTERN NEUROLOGICAL ASSOCIATES
Lumbar Spine CT Scans 6
WESTERN JOURNAL OF MEDICINE, THE
Subscription 51
WISELY FOODS
Saffola Margarine 58
WYETH LABS
Ativan Oral 25, 26
Lo-Ovral 17, 18

Bactrim™
(trimethoprim and sulfamethoxazole/Roche)
succeeds

Bactrim is useful for the following infections when due to susceptible strains of indicated organisms (see indications section in summary of product information):

Expanding its usefulness in antimicrobial therapy



in recurrent UTI...
a continuing record of high clinical effectiveness against common uropathogens

in acute otitis media in children...
effective against both major otic pathogens...with *b.i.d.* convenience

in acute exacerbations of chronic bronchitis in adults...
clears the sputum and lowers its volume...on *b.i.d.* dosage

in shigellosis...
relieves diarrhea due to susceptible *Shigella* organisms

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)
Before prescribing, please consult complete product information, a summary of which follows:
Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note.* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.
For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.
For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.
For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.
Also for the treatment of documented *Pneumocystis carinii* pneumonitis.
Contraindications: Hypersensitivity to trimethoprim or sulfonamides, patients with documented megaloblastic anemia due to folate deficiency, pregnancy at term, nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus, infants less than 2 months of age.
Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A *b*-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended, therapy should be discontinued if a significantly reduced count of any formed blood element is noted.
Precautions: *General.* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin, reassess coagulation time when administering Bactrim to these patients.
Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.
Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.
Dosage: Not recommended for infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN
Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.
Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.
For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.
ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS
Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.
PNEUMOCYSTIS CARINII PNEUMONITIS
Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.
Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml), fruit-licorice flavored—bottles of 16 oz (1 pint).

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Division of Hoffmann-La Roche Inc
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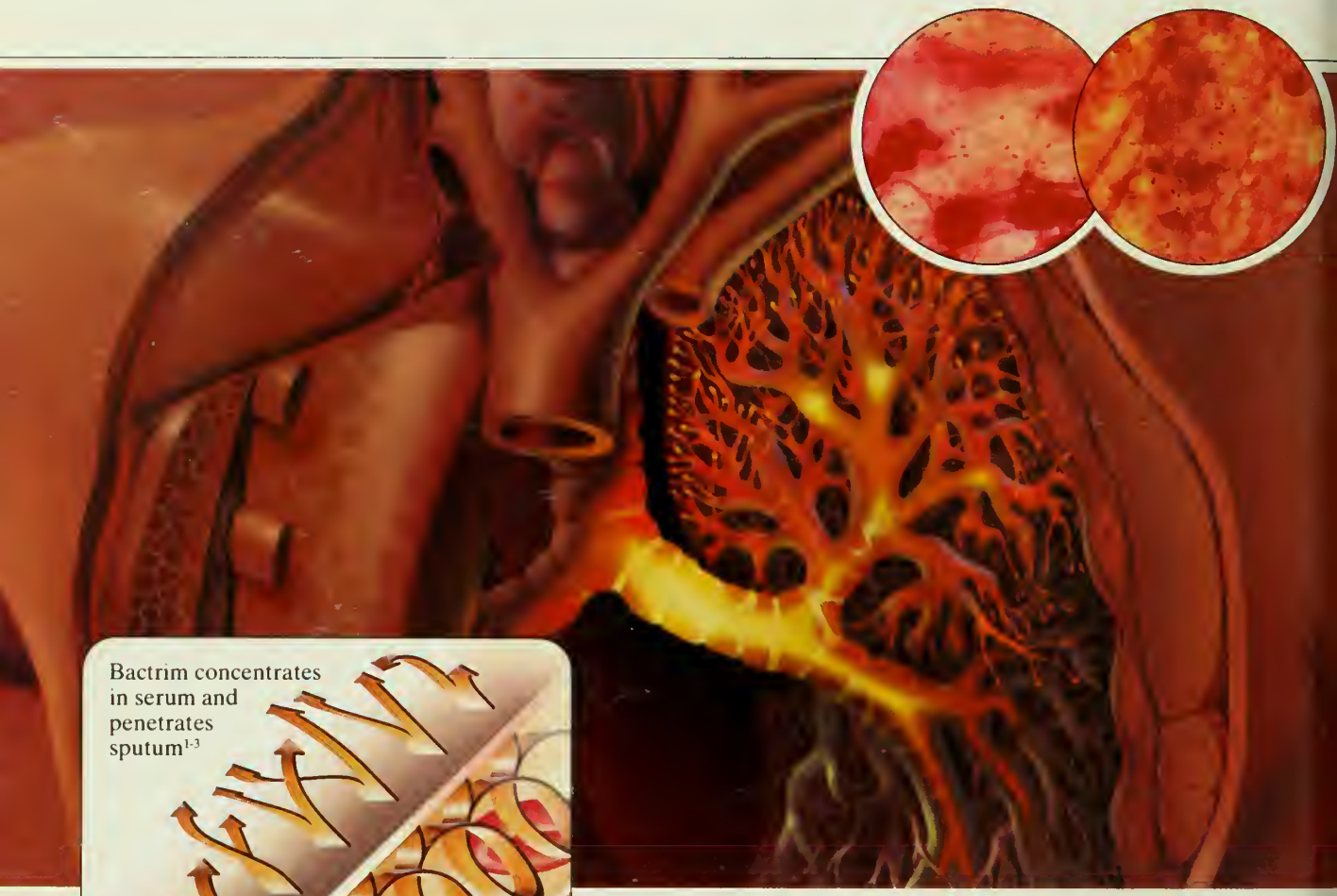
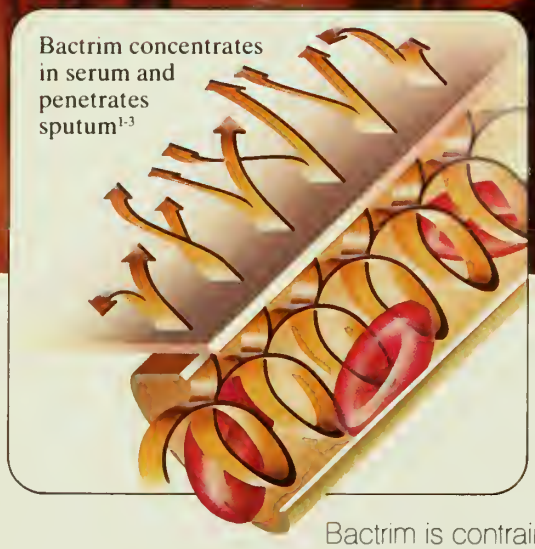
Bactrim™ (trimethoprim and sulfamethoxazole/Roche)
attacks the major pathogens in acute exacerbations of chronic bronchitis*

attacks *H. influenzae*—even ampicillin-resistant strains attacks *S. pneumoniae*





Bactrim is effective *in vitro* against most strains of both *S. pneumoniae* and *H. influenzae*—even ampicillin-resistant strains. In acute exacerbations of chronic bronchitis involving these two pathogens, sputum cultures taken seven days after a two-week course of therapy showed that Bactrim eradicated these bacteria in 91% (50 of 55) of the patients treated.[4]

Bactrim is contraindicated in pregnancy at term and nursing mothers, infants under two months of age, patients with documented megaloblastic anemia due to folate deficiency and those hypersensitive to either component.

References: **1.** Hughes DTD, Bye A, Hodder P. *Adv Antimicrob Antineoplastic Chemother 1/2*:1105-1106, 1971. **2.** Jordan GW *et al. Can Med Assoc J 112*:91S-95S, Jun 14, 1975. **3.** Beck H, Pechere JC: *Prog Antimicrob Anticancer Chemother 1*:663-667, 1969. **4.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In acute exacerbations of chronic bronchitis* in adults

economical *b.i.d.*

Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole/Roche)

Please see preceding page for summary of product information.

*Due to susceptible organisms, when it offers an advantage over single-agent antibacterials.

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THE WESTERN Journal of Medicine

VOLUME 137 • NUMBER 5 **NOVEMBER 1982**

ORIGINAL ARTICLES

365 Campylobacter *Enteritis: A Large Outbreak Traced to Commercial Raw Milk*
DAVID N. TAYLOR, MD; BRUCE W. PORTER, MPA; CYNTHIA A. WILLIAMS, BS; HILLARY G. MILLER; CHERYL A. BOPP, BS, and PAUL A. BLAKE, MD

370 *Middle Ear Effusion in Children: A Report of Treatment in 500 Cases*
BRIAN D. FORQUER, MS, and FRED H. LINTHICUM, Jr, MD

375 *Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis*
RICHARD D. PEZNER, MD, and JAMES A. LIPSETT, MD

MEDICAL PROGRESS

379 *Fasting: The History, Pathophysiology and Complications*
PETER R. KERNDT, MD; JAMES L. NAUGHTON, MD; CHARLES E. DRISCOLL, MD, and DAVID A. LOXTERKAMP, MD

MEDICAL STAFF CONFERENCE

400 Pneumocystis *Lung Disease in Homosexual Men* Chief Discussant: JEFFREY GOLDEN, MD

EPITOMES OF PROGRESS

408 *Orthopedics—Important Advances in Clinical Medicine*

EDITORIALS

417 • *Is It Time for a Fundamental Reexamination of Medical Education?* • *Fasting* • *Acquired Immune Dysfunction in Homosexual Men* • *How About Organizing 'Friends of Medicine'?* • *Overdose With Tricyclic Antidepressants*

CASE REPORTS

425 *Admission Criteria for Tricyclic Antidepressant Ingestion* MICHAEL CALLAHAM, MD

429 *Hypervitaminosis A—A Cause of Hypercalcemia* SUNITA C. BAXI, MD, and GEORGE E. DAILEY III, MD

431 *Survival After Intracerebral Hemorrhage in Wegener's Granulomatosis*
CHRISTOPHER BAILLIE HEARNE, MD, and EDWARD T. ZAWADA, Jr, MD

CORRESPONDENCE

435 • *Differential Diagnosis of Pleural Effusions* • *AMA and a National Health Policy* • Ascaris *Infection in Washington State* • *Usefulness of IDA Scanning* • *Nuclear Armaments* • *Sherlock in the Emergency Room* • *Serendipitous Diagnosis of Multiple Myeloma by Hemoglobin Electrophoresis* • *Leukemia in Hospital Patients With Occupational Exposure to the Sawmill Industry* • *High Rock, High Tech and Karl Marx* • *A Distinction in Terminology*

TOPICS IN PRIMARY CARE MEDICINE

443 *Kicking the Habit: Benefits and Methods of Quitting Cigarette Smoking* STEVEN R. CUMMINGS, MD

HEALTH CARE DELIVERY

448 *Physician Behavior Modification Using Claims Data: Tetracycline for Upper Respiratory Infection*
THOMAS S. McCONNELL, MD; ALICE H. CUSHING, MD; ARTHUR D. BANKHURST, MD; JAMES L. HEALY, MA; PATRICIA A. McILVENNA, MA, and BETTY J. SKIPPER, PhD

MEDICINE IN PERSPECTIVE

451 *Medical Adventure in South America* WILLIAM L. MINKOWSKI, MD, MPH

SPECIAL ARTICLE

460 *Anatomy, Physiology and Pathology of Biomedical Information* HAROLD M. SCHOOLMAN, MD

INFORMATION

467 *Scope of Practice* C. JOHN TUPPER, MD

468 *Sources of Supply of Selected Immunobiologics: 1982* S. BENSON WERNER, MD

471 *Book Reviews* • *Books Received, See Advertising Page 50*

476 *In Memoriam*

Medical Practice Questions, See Pages 374, 447, 450 and 459
Detailed Table of Contents, See Advertising Pages 7 and 11
Information for Authors, See Advertising Page 46

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA, HAWAII AND NEVADA; ALASKA; IDAHO; MONTANA; NEW MEXICO; OREGON; UTAH; WASHINGTON; WYOMING (See Advertising Page 15)**

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society**

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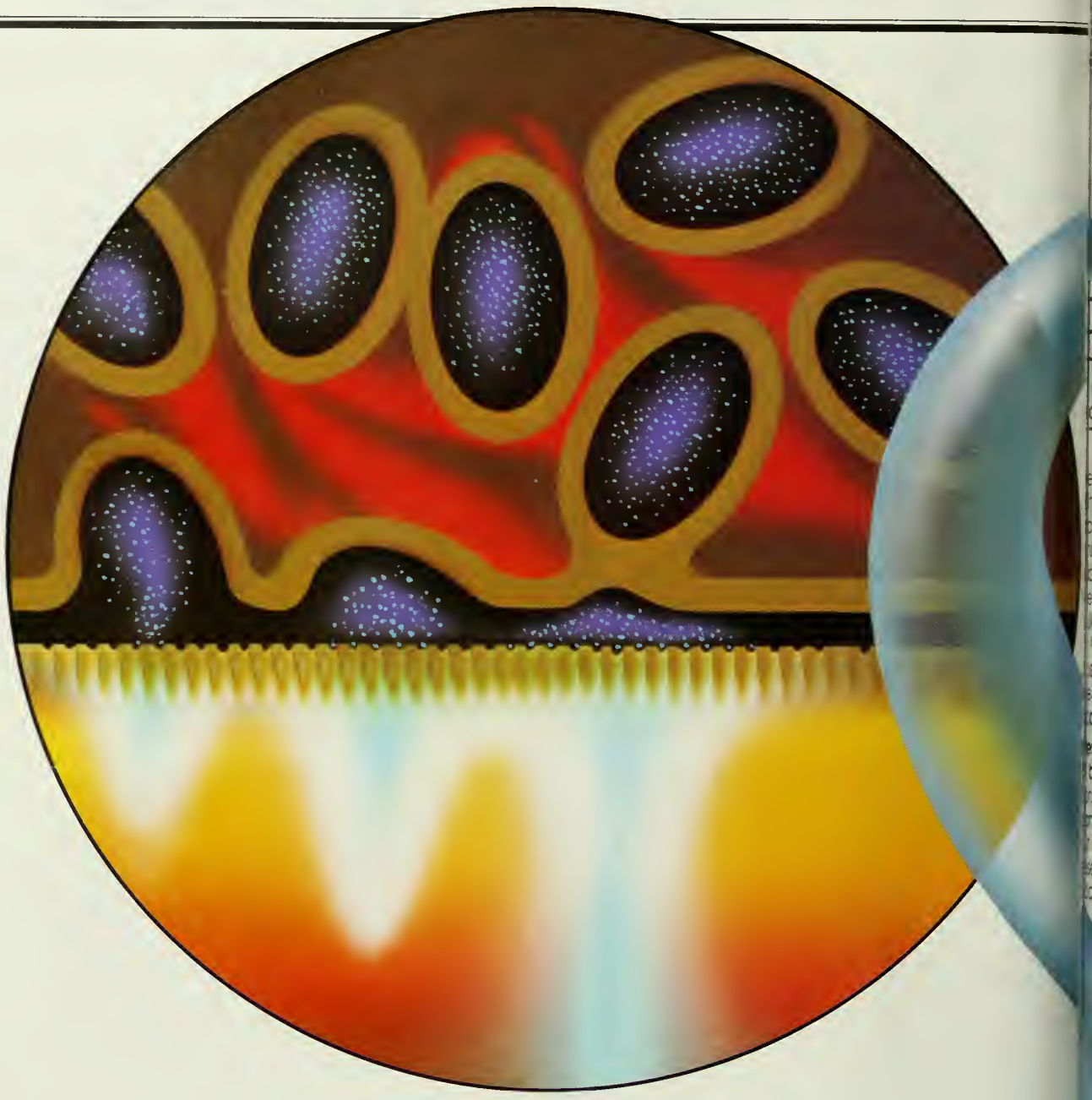
VALIUM® (diazepam/Roche) IN THE FOREFRONT OF NEURORECEPTOR RESEARCH



Artist's concept of neurotransmitter being released into synaptic cleft and impinging on receptor sites

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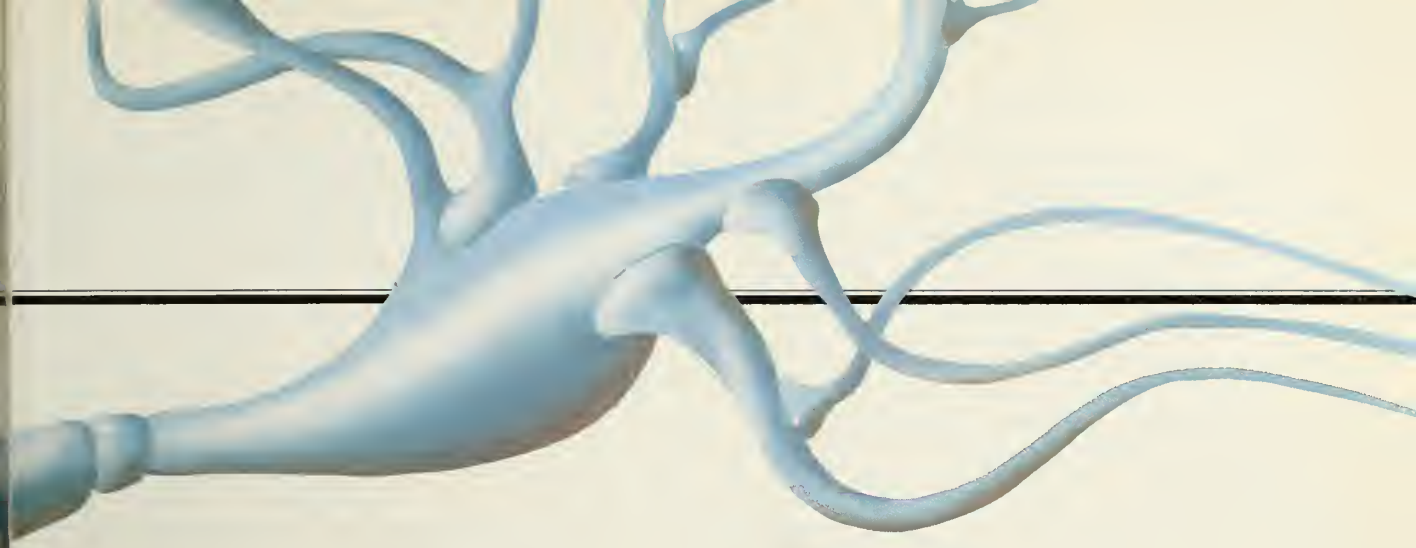

)pening new investigative pathways ıto where and how Valium (diazepam/Roche) exerts ıs distinctive antianxiety action

ew discoveries in receptor research have mulated the search for endogenous brain sub-ınces that may be involved in the mediation of xiety.[1-5] It has been further theorized that these ɔstances may act as ligands that bind to e same or similar sites as do benzodiazepine mole-les[5,6]—binding sites early identified with the use ^{3}H-diazepam.[5,7] These binding sites are now stulated to be benzodiazepine receptors, since e ability of benzodiazepines to bind with the sites pears to correlate with their clinical effects.[2,4,7,8]

esent investigations into clinical relevance binding sites. Laboratories at Roche have nducted research to identify and isolate sub-ınces that may prove to be endogenous ligands, t no definitive identification has yet been made. Rsearchers are also studying substances which o not bind, but rather interact with the benzo-diazepine binding sites—most notably gamma-aminobutyric acid (GABA)—and are postulated to mediate certain pharmacologic and clinical benzodiazepine effects.[2-4,9,10]

Under especially intense investigations are the GABA receptors and the benzodiazepine binding sites themselves—apparently constellations of closely linked but not identical structures.[8]

Future implications for improved therapy. In future work, Roche researchers and other scientists hope to identify and characterize various differential sites in the brain, which may result in more specific diagnostic and therapeutic approaches.

2-mg, 5-mg, 10-mg scored tablets

Valium® (IV)

diazepam/Roche

THE RESEARCH AND CLINICAL LEADER

Please see brief summary of product information and references on the following page.

ROCHE®

VALIUM® IV
(diazepam/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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References: **1.** Tallman JF *et al: Science 207*:274-281, Jan 18, 1980. **2.** Bunney WE Jr: *Psychiatr Ann 11*:11-15, Jan 1981. **3.** Davis JM *et al: J Clin Psychiatry 42*(11) Sec 2:4-14, Nov 1981. **4.** Study RE, Barker JL: *JAMA 247*: 2147-2151, Apr 16, 1982. **5.** Braestrup C, Nielsen M, Olsen CE: *Proc Natl Acad Sci USA 77*:2288-2292, Apr 1980. **6.** Basmann HB, Case KR, DiStefano P: *FEBS Lett 82*:368-372, Oct 1977. **7.** Braestrup C, Albrechtsen R, Squires RF: *Nature 269*:702-704, Oct 20, 1977. **8.** Snyder SH: *Psychosomatics 22*:986-989, Nov 1981. **9.** Rickels K: *J Clin Psychiatry 42*(11) Sec 2:40-44, Nov 1981. **10.** Haefely WE: *Br J Psychiatry 133*:231-238, Sep 1978.

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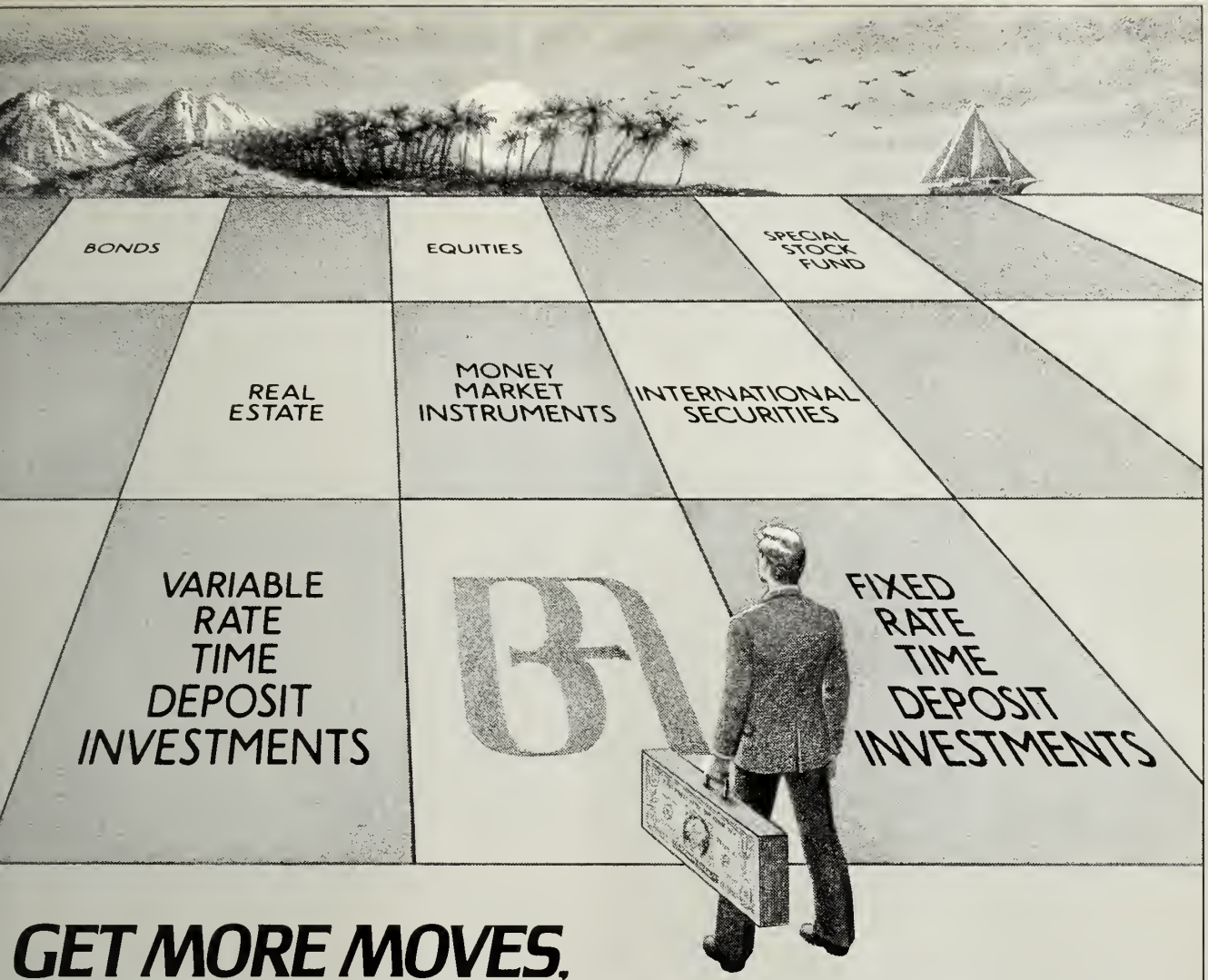

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VOLUME 137 • NUMBER 5 **NOVEMBER 1982**

TABLE OF CONTENTS

ORIGINAL ARTICLES

365 Campylobacter *Enteritis: A Large Outbreak Traced to Commercial Raw Milk*
DAVID N. TAYLOR, MD; BRUCE W. PORTER, MPA; CYNTHIA A. WILLIAMS, BS; HILLARY G. MILLER; CHERYL A. BOPP, BS, and PAUL A. BLAKE, MD
From the Enteric Bacteriology and Epidemiology Branch, Center for Infectious Diseases, Centers for Disease Control, US Public Health Service, US Department of Health and Human Services, Atlanta; the Pima County Health Department, Tucson, and the Arizona State Department of Health Services, Phoenix.

370 *Middle Ear Effusion in Children: A Report of Treatment in 500 Cases*
BRIAN D. FORQUER, MS, and FRED H. LINTHICUM, Jr, MD
From the Otologic Medical Group, Los Angeles.

375 *Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis*
RICHARD D. PEZNER, MD, and JAMES A. LIPSETT, MD
From the Division of Radiation Oncology, City of Hope National Medical Center, Duarte, California.

MEDICAL PROGRESS

379 *Fasting: The History, Pathophysiology and Complications*
PETER R. KERNDT, MD; JAMES L. NAUGHTON, MD; CHARLES E. DRISCOLL, MD, and DAVID A. LOXTERKAMP, MD
From the Department of Medicine, University of California, San Francisco, and the Department of Family Practice, University of Iowa College of Medicine, Iowa City.

MEDICAL STAFF CONFERENCE

400 Pneumocystis *Lung Disease in Homosexual Men* Chief Discussant: JEFFREY GOLDEN, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was prepared by Drs. David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

EPITOMES OF PROGRESS

Orthopedics—Important Advances in Clinical Medicine
Items of progress in orthopedics. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

408 *Injection of Steroid Agents in Solitary Bone Cysts* TILLMAN M. MOORE, MD
409 *Methacrylate Cementation for Giant Cell Tumor* TILLMAN M. MOORE, MD
409 *Limb Replantation* ROY A. MEALS, MD
410 *Foot Problems in Diabetes Mellitus* GILBERT WRIGHT, MD
410 *The Treatment of Acetabular Fractures* DAVID H. GERSHUNI, MD, FRCS
411 *Rattlesnake Bites: Current Hospital Therapy* STEVEN R. GARFIN, MD
412 *Spinal Stenosis* GRAHAM A. PURCELL, MD
412 *Vascularized Bone Grafts* GARY K. FRYKMAN, MD
413 *The Role of Hyperbaric Oxygen in Orthopedics* MICHAEL B. STRAUSS, MD
414 *Surgical Management of Scoliosis* WILLIAM C. McMASTER, MD
415 *Orthopedic Management of Patients With Multiple Injuries* PETER G. TRAFTON, MD
415 *Arthroscopic Surgical Techniques* CHARLES R. STROTZ, MD

EDITORIALS

417 *Is It Time for a Fundamental Reexamination of Medical Education?*

418 *Fasting* THOMAS J. MERIMEE, MD
Dr. Merimee is Director, Division of Endocrinology and Metabolism, and Professor of Medicine, Department of Medicine, University of Florida College of Medicine, Gainesville.

419 *Acquired Immune Dysfunction in Homosexual Men* ARTHUR J. AMMANN, MD
From the Pediatric Immunology-Rheumatology Division, Pediatric Clinical Research Center, University of California, San Francisco.

421 *How About Organizing 'Friends of Medicine'?*

422 *Overdose With Tricyclic Antidepressants* RENE A. LANGOU, MD
Dr. Langou is Associate Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut.

CASE REPORTS

425 *Admission Criteria for Tricyclic Antidepressant Ingestion* MICHAEL CALLAHAM, MD
From the Emergency Medicine Department, Highland General Hospital, Oakland, California, and the Department of Medicine, University of California, San Francisco.

429 *Hypervitaminosis A—A Cause of Hypercalcemia* SUNITA C. BAXI, MD, and GEORGE E. DAILEY III, MD
From the Division of Diabetes and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, California.

431 *Survival After Intracerebral Hemorrhage in Wegener's Granulomatosis*
CHRISTOPHER BAILLIE HEARNE, MD, and EDWARD T. ZAWADA, Jr, MD
From the Department of Medicine, University of Utah School of Medicine, and the Veterans Administration Medical Center, Salt Lake City.

(Continued on Page 11)

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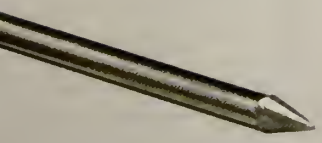

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IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery since propranolol is a competitive inhibitor of beta-receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.* CHRONIC BRONCHITIS, EMPHYSEMA), propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

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Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

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The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers. Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular* bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands, arterial insufficiency, usually of the Raynaud type, thrombocytopenic purpura.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous. reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal.* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System. dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic. leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular. orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity. purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

Other. hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

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(Continued from Page 7)

Differential Diagnosis of Pleural Effusions

435 PREETHAM KONDLAPOODI, MD, and JUAN B. GABRIEL, Jr, MD

435 JAMES B. D. MARK, MD

436 *AMA and a National Health Policy* JOSEPH F. BOYLE, MD

436 Ascaris *Infection in Washington State*
PHYLLIS SHOEMAKER-NAWAS, BA; FLOYD FROST, PhD; JOHN KOBAYASHI, MD, MPH, and PHILLIP JONES, MD, MPH

437 *Usefulness of IDA Scanning* JEFFREY L. KAUFMAN, MD

Nuclear Armaments

437 CHRISTINE K. CASSEL, MD

438 RICK LESKOWITZ, MD

438 *Sherlock in the Emergency Room* J. S. GRISOLIA, MD, and W. C. WIEDERHOLT, MD

439 *Serendipitous Diagnosis of Multiple Myeloma by Hemoglobin Electrophoresis* DENNIS A. CASCIATO, MD

440 *Leukemia in Hospital Patients With Occupational Exposure to the Sawmill Industry* JOHN A. BURKART, PhD

441 *High Rock, High Tech and Karl Marx* E. R. W. FOX, MD

442 *A Distinction in Terminology* JOEL A. STETTNER, MD

TOPICS IN PRIMARY CARE MEDICINE

443 *Kicking the Habit: Benefits and Methods of Quitting Cigarette Smoking* STEVEN R. CUMMINGS, MD
From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco.

HEALTH CARE REVIEW

448 *Physician Behavior Modification Using Claims Data: Tetracycline for Upper Respiratory Infection*
THOMAS S. McCONNELL, MD; ALICE H. CUSHING, MD; ARTHUR D. BANKHURST, MD; JAMES L. HEALY, MA, PATRICIA A. McILVENNA, MA, and BETTY J. SKIPPER, PhD
From the New Mexico Professional Standards Review Organization, Ambulatory Care Demonstration Project, Albuquerque.

MEDICINE IN PERSPECTIVE

451 *Medical Adventure in South America* WILLIAM L. MINKOWSKI, MD, MPH

SPECIAL ARTICLE

460 *Anatomy, Physiology and Pathology of Biomedical Information* HAROLD M. SCHOOLMAN, MD
Dr. Schoolman is Deputy Director for Research and Education, National Library of Medicine, Bethesda, Maryland.

INFORMATION

467 *Scope of Practice* C. JOHN TUPPER, MD
Dr. Tupper is Professor, Departments of Internal Medicine, Community Health and Family Practice, University of California, Davis, School of Medicine, Davis, and Chairman of the California Medical Association Commission on State Legislation.

468 *Sources of Supply of Selected Immunobiologics: 1982* S. BENSON WERNER, MD
From the Infectious Disease Section, California Department of Health Services, Berkeley.

BOOK REVIEWS

471 *The Elbow* Edited by THOMAS G. WADSWORTH, MChOrth, FRCS, FRCSE
Reviewed by MARVIN B. HAYS, MD

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By C. HENRY KEMPE, MD; HENRY K. SILVER, MD; DONOUGH O'BRIEN, MD, FRCP, and Associate Authors
Reviewed by PAUL F. WEHRLE, MD

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Reviewed by RALPH W. HALE, MD

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By DOUGLAS W. HENDERSON, MB, BS, FRCPA, and JOHN M. PAPADIMITRIOU, MD, PhD, MRCPath, FRCPA
Reviewed by EDWARD A. SMUCKLER, MD, PhD

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Reviewed by BEVERLY C. MORGAN, MD

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Reviewed by MARION NESTLE, PhD

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By MARCUS A. KRUPP, MD; LAWRENCE M. TIERNEY, Jr, MD; ERNEST JAWETZ, MD, PhD; ROBERT L. ROE, MD, and CARLOS A. CAMARGO, MD
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Reviewed by ILZA VEITH, PhD, DmedSci

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Edited by W. MAXWELL COWAN, MD, Editor; and ZACH W. HALL, PhD, and ERIC R. KANDEL, MD, Associate Editors
Reviewed by GEORGE K. YORK, MD

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By EDWARD J. QUILLIGAN, MD, and FREDERICK ZUSPAN, MD; With Contributions by WILLIAM J. LEDGER, MD; BARRY S. SCHIFRIN, MD, and FEIZAL WAFFARN, MD
Reviewed by MORTON A. STENCHEVER, MD

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Reviewed by LOUIS BORGENICHT, MD

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Reviewed by H. HARRISON SADLER, MD

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Edited by LLOYD H. SMITH, Jr, MD, and SAMUEL O. THIER, MD
Reviewed by GEORGE A. PORTER, MD

476 *In Memoriam*

Medical Practice Questions, See Pages 374, 447, 450 and 459
Information for Authors, See Advertising Page 46
Books Received, See Advertising Page 50
Subscription Information, See Advertising Page 57

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Adverse Reactions: The most consistent adverse reactions are usually due to overdose and are
Gastrointestinal. Nausea, vomiting, epigastric pain, hematemesis, diarrhea.
Central Nervous System. Headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions
Cardiovascular Palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life threatening ventricular arrhythmias.
Respiratory Tachypnea
Renal: Albuminuria, increased excretion of renal tubular cells and red blood cells, potentiation of diuresis
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ANESTHESIOLOGY

January 6-9—**Anesthesia Update—1983.** UCSD at Vacation Village, San Diego. Thursday-Sunday. 20 hrs. $250. Contact: Jordan Katz, MD, Dept. of Anesthesia (M-004), UCSD, La Jolla 92093. (714) 453-7500, ext. 3292.

February 4-6—**21st Clinical Conference in Pediatric Anesthesiology.** Childrens Hospital at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $175. Contact: Wayne Herbert, MD, Childrens Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 669-2262.

February 13-18—**11th Obstetric Anesthesia Conference.** Ohio State University at Maui Surf Hotel, Maui, and Sheraton Waikiki, Oahu. Sunday-Friday. 25 hrs. Contact: Ohio State Univ. Hospitals, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, OH 43210. (614) 421-8487.

CANCER

November 17—**Controversies in the Management of Early Breast Cancer.** Hospital of the Good Samaritan at Biltmore, Los Angeles. Wednesday. 6 hrs. Contact: Bonnie VanWaardenburg, Dept. of Ed., 616 S. Witmer St., Los Angeles 90017. (213) 977-2345.

December 8—**18th Annual Northern California Cancer Conference.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: N. T. Enloe Mem. Hosp., Cont. Ed. Office, W. 5th Ave and The Esplanade, Chico 95926. (916) 891-7375.

January 14-15—**Urological Cancer Symposium.** USC and Los Angeles Urological Society at USC. Friday-Saturday. 21 hrs. Contact: Trudy Mackel, 1940 Turrell St., Lomita 90717. (213) 326-7418.

February 4-6—**Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 15-18—**Clinical Hematology and Oncology.** See Medicine, February 15-18.

March 5-6—**Hyperthermia and Radiation Therapy in the Treatment of Cancer—18th Annual Cancer Symposium.** West Coast Cancer Foundation at Sheraton Palace, San Francisco. Saturday-Sunday. 12 hrs. $115 before Feb. 1; $140, thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

March 9-11—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont, San Francisco. Wednesday-Friday.

EMERGENCY MEDICINE

December 4—**Emergency Pediatrics, Part II.** See Pediatrics, December 4.

December 13-17—**Postgraduate Institute for Emergency Physicians—Symposium II.** UCSD at Hilton, San Diego. Monday-Friday. 33 hrs. $425.

January 17-21—**Postgraduate Institute for Emergency Physicians—Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs. $425.

January 22-29—**Advanced Problems in Cardiac Emergencies.** UCSD, American Inst. of Postgraduate Education and Scripps Mem. Hosp. at Kona Surf Hotel, Kona. One week. 21 hrs. $325. Contact: AIPE, P.O. Box 2101, Del Mar 92014. (714) 454-3212.

January 28-30—**Advanced Cardiac Life Support Workshop.** Emergency Medical Associates at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

January 31-February 4—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

March 6-11—**Emergency Medicine: 1983.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 24 hrs.

(Continued on Page 25)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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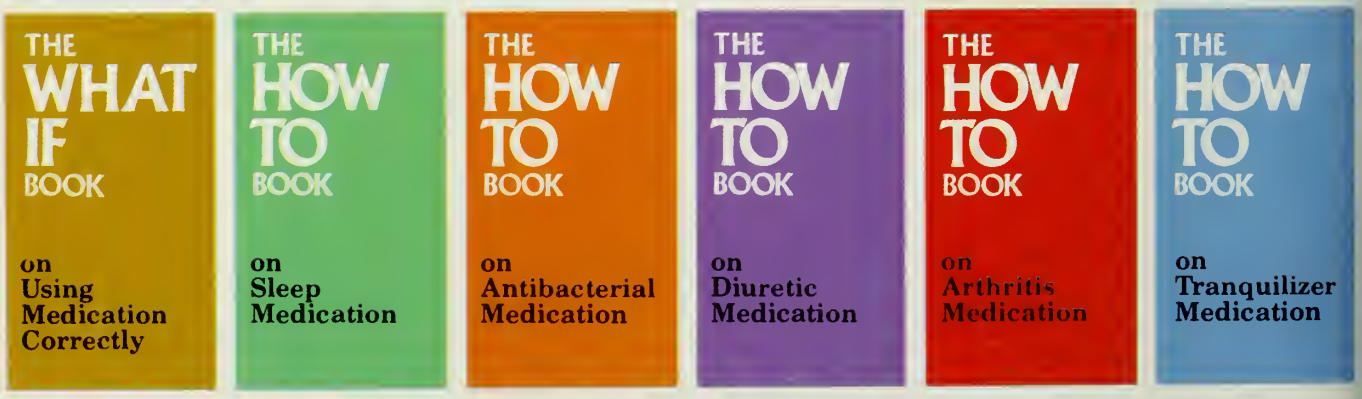

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RU-TUSS®

EXPECTORANT

Each fluid ounce contains: Codeine Phosphate 65.8 mg • (WARNING: MAY BE HABIT FORMING) Phenylephrine Hydrochloride 30 mg • Phenylpropanolamine Hydrochloride 20 mg • Pheniramine Maleate 20 mg • Pyrilamine Maleate 20 mg • Ammonium Chloride 200 mg • Alcohol 5%

Symptomatic Relief of Coughing with Nasal and Bronchial Decongestion

Full range symptom-reliever for patients with air way congestion in the upper chest as well as the nose and throat.
• Blocks the cough • Loosens mucus
• Reduces sneezing • Eases breathing
• Tasty, so it's easy to take

To Relieve the Symptoms of Winter Weather Upper Respiratory Distres

RU-TUSS®/RU-TUSS®

TABLETS EXPECTORANT

RU-TUSS®

Tablets

DESCRIPTION

Each prolanged action tablet contains:

Phenylephrine Hydrochloride	25 mg
Phenylpropanolamine Hydrochloride	50 mg
Chlorpheniramine Maleate	8 mg
Hyoscyamine Sulfate	0.19 mg
Atropine Sulfate	0.04 mg
Scapolamine Hydrobromide	0.01 mg

Ru-Tuss Tablets act continuously for 10 to 12 hours

Ru-Tuss Tablets are an oral antihistaminic, nasal decongestant and anti-secretory preparation.

INDICATIONS AND USAGE Ru-Tuss Tablets provide relief of the symptoms resulting from irritation of sinus, nasal and upper respiratory tract tissues Phenylephrine and phenylpropanalamine combine to exert a vasaconstrictive and decongestive action while chlorpheniramine maleate decreases the symptoms of watering eyes, post nasal drip and sneezing which may be associated with an allergic-like response The belladonna alkaloids, hyoscyomine, atropine and scopolamine further augment the anti-secretory activity of Ru-Tuss Tablets

CONTRAINDICATIONS Hypersensitivity to antihistamines or sympathomimetics Ru-Tuss Tablets are contraindicoted in children under 12 years of age and in patients with glaucoma, bronchial asthma and women who are pregnant Concomitant use of MAO inhibitors is contraindicated

WARNINGS Ru-Tuss Tablets may cause drowsiness Patients should be warned of the possible additive effects caused by taking antihistamines with alcohol, hypnotics, sedatives or tranquilizers

PRECAUTIONS Ru-Tuss Tablets contain belladonna alkaloids, and must be administered with care to those patients with glaucoma, or urinary bladder neck obstruction Caution should be exercised when Ru-Tuss Tablets are given to patients with hypertension, cardiac or peripheral vascular disease or hyperthyroidism Patients should avoid driving a motor vehicle or operating dangerous machinery (See Warnings).

OVERDOSAGE Since the action of sustained release products may continue for as long as 12 hours, treatment of overdoses directed at reversing the effects of the drug and supporting the patient should be maintained for at least that length of time Saline cathartics are useful for hastening evacuation of unreleased medication in children and infants, antihistamine overdosage may produce convulsions and death.

ADVERSE REACTIONS Hypersensitivity reactions such os rash, urticaria, leukopenia, agranulocytosis, and thrombacytopenia may occur Other adverse reactions to Ru-Tuss Tablets may be drowsiness, lassitude, giddiness, dryness of the mucous membranes, tightness of the chest, thickening of bronchial secretions, urinary frequency and dysuria, palpitation, tachycardia, hypotension hypertension, faintness, dizziness, tinnitus, headache, incoordination, visual disturbances, mydriasis, xerotomia, blurred vision, anorexia nausea, vomiting, diarrheo, constipation, epigastric distress, hyperirritability, nervousness, dizziness and insomnia Large overdoses may cause tachypnea, delirium, fever, stupor, coma and respiratory failure

DOSAGE AND ADMINISTRATION Adults and children over 12 years of age, one tablet morning and evening Not recommended for children under 12 years of oge Tablets are to be swallowed whole

HOW SUPPLIED:

Bottles of 100 Tablets	NDC 0524-0058-01
Bottles of 500 Tablets	NDC 0524-0058-05

Federal law prohibits dispensing without prescription

DISTRIBUTED BY:
Boots Pharmaceuticals, Inc.
Shreveport, Louisiana 71106

MANUFACTURED BY:
Vitarine Company, Inc.
Springfield Gardens, New York 11413

RU-TUSS®

Expectorant

DESCRIPTION

Each fluid ounce of Ru-Tuss Expectorant contains:

Codeine Phosphate	65
(WARNING: MAY BE HABIT FORMING)	
Phenylephrine Hydrochloride	3
Phenylpropanolamine Hydrochloride	2
Pheniramine Maleate	2
Pyrilamine Maleate	2
Ammonium Chloride	20
Alcohol	

Ru-Tuss Expectorant is an oral antifussive, antihistaminic, nasal decongestant and ex torant preparation

INDICATIONS AND USAGE Ru-Tuss Expectorant is indicated for symptomatic relief of respiratory congestion associated with pharyngitis, tracheitis, bronchitis, and allergic tis Also, for the temporary relief of symptoms associated with hay fever, allergies, congestion and cough due to the common cold

CONTRAINDICATIONS Hypersensitivity to antihistamines Concomitant use of an hypertensive or antidepressant drug containing a monoamine oxidase inhibi contraindicated.

Ru-Tuss Expectorant is contraindicated in patients with glaucoma, bronchial asthm in women who are pregnant

WARNINGS Ru-Tuss Expectorant contains codeine phosphate, therefore, the patient s be warned of the potential that this drug may be habit forming Ru-Tuss Expectoran cause drowsiness Patients should be warned of the possible additive effect caus taking antihistamines with alcohol, hypnotics, sedatives and tronquilizers

PRECAUTIONS Patients taking Ru-Tuss Expectorant should avoid driving a motor veh operating dangerous machinery (See Warnings). Caution should be taken with pa having hypertension, diabetes, hyperthyroidism and cardiovascular disease.

Caution should also be used in patients with pulmonary, hepatic or renal insufficien

ADVERSE REACTIONS Ru-Tuss Expectorant may cause drowsiness, lassitude, gidd dryness of mucous membranes, tightness of the chest, thickening of bronchiol secre urinary frequency and dysuria, palpitation, tachycardia, hypotension/hypertension, ness, dizziness, tinnitus, headache, incoordination, visual disturbances, mydriasis, stomia, blurred vision, anorexia, nausea, vomiting, diarrhea, constipation, epigastr tress, hyperirritability, nervousness, and insomnia Overdoses may cause restles excitation, delirium, tremors, euphoria, metabolic acidosis, stupor, tachycardia and convulsions

DOSAGE AND ADMINISTRATION Adults, 1 or 2 teospoonfuls, orally, every 4 hours, exceed 10 teaspoonfuls in any 24-hour period

Children 6 to 12 years of age: ½ the adult dose, not to exceed 6 teaspoonfuls 24-hour period Children 2 to 6 years of age ½ teaspoonful every 4 hours, n exceed 3 teaspoonfuls in any 24-hour period Children under 2 years of age U directed by a physician

HOW SUPPLIED: (16 fl oz)

Pint Bottles	NDC 0524-10

Federal law prohibits dispensing without prescription.

MANUFACTURED AND DISTRIBUTED BY:
Boots Pharmaceuticals, Inc.
Shreveport, Louisiana 71106

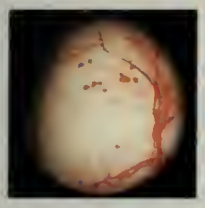
Boots Pharmaceuticals, Inc.
Shreveport, Louisiana 71106
Pioneers in medicine for the family

WE HAVE A SOLUTION FOR A DIFFICULT UROLOGICAL PROBLEM

The Problem

SYMPTOMS:

EARLY
INTERSTITIAL CYSTITIS



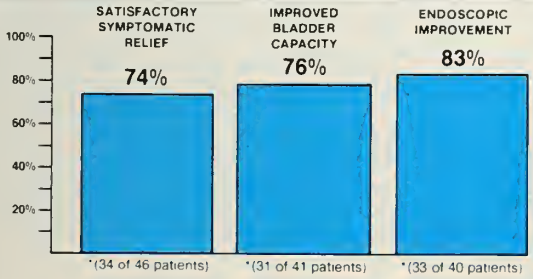
CLASSICAL
INTERSTITIAL CYSTITIS

- ☐ irritative voiding symptoms
- ☐ suprapubic pain
- ☐ functional bladder capacity reduced
- ☐ anatomical bladder capacity:
  - EARLY — normal
  - CLASSICAL — reduced
- ☐ vesical mucosa:
  - EARLY — normal appearing
  - CLASSICAL — ulcerated, scarred
- ☐ submucosal vesical hemorrhages observed following second overdistension

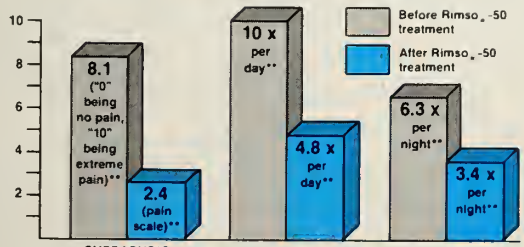
DIAGNOSIS: INTERSTITIAL CYSTITIS

The Solution

Rimso®-50
brand of
STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE



*STEWART, B.H., et al., J. Urol., 36:116, 1976



** Data on File — Research Industries Corporation

FOR FURTHER INFORMATION WJ 11/82

RESEARCH INDUSTRIES CORPORATION
1847 West 2300 South
Salt Lake City, Utah 84119
Toll-Free 1-800-453-8432

Name

Address

City State Zip

Rimso®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE: Rimso®-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso®-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS: None known.

WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso®-50. The physician should be cognizant of this possibility in prescribing Rimso®-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso®-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso®-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide. The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

DOSAGE AND ADMINISTRATION: Instillation of 50 ml of Rimso®-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of Rimso®-50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia. (Saddle block has been suggested.)

HOW SUPPLIED:
Bottles contain 50 ml of sterile and pyrogen-free Rimso®-50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (15° to 30° C).
Do not autoclave.
NDC #0433-0433-05

*Stewart, B.H., et al., J. Urol., 36:116, 1976

NEW PRODUCT

Rimso®-100
brand of
STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE

CRYOPRESERVATIVE SOLUTION
(99.0 + concentration)

Available in:
- 10 ml ampules, 10 ampules/case
- 70 ml bottles, 6 bottles/case
- 70 ml multi-dose containers, 6 bottles/case

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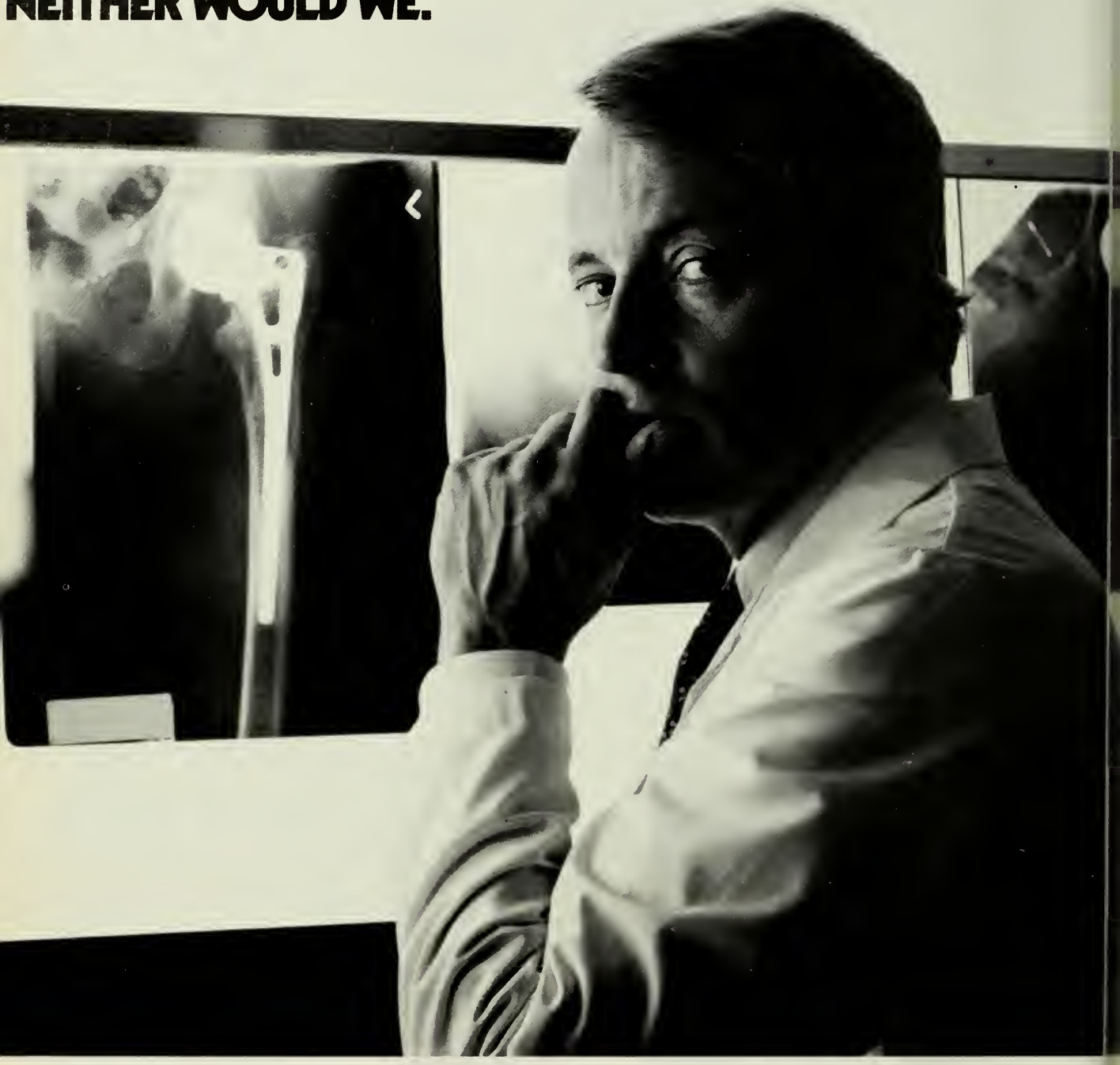

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OFFERING MEDICAL MALPRACTICE INSURANCE
TO DOCTORS IN
CALIFORNIA, NEVADA, WYOMING AND MONTANA

(Continued from Page 15)

March 13-18—**Fourth Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses Assn. at Mammoth Lakes. Sunday-Friday. 23 hrs. $325. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 14-18—**Postgraduate Institute for Emergency Physicians—Symposium II.** UCSD. Monday-Friday. 33 hrs. $425.

MEDICINE

December 3-4—**Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday-Saturday. 15 hrs. $150.

December 3-5—**Perioperative Cardiac Dysfunction.** Cardiothoracic Research and Education Foundation at Hilton Beach and Tennis Resort, San Diego. Friday-Sunday. 16 hrs. $250. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

December 3-5—**Clinical Management of Coronary Disease and Dual-Mode Exercise Testing.** International Medical Education Corp. at MGM Grand, Las Vegas. Friday-Sunday. 13 hrs. $260. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr., Englewood, CO 80112. (800) 525-8651.

December 4-5—**MKSAP VI Review Course—Internal Medicine Review Part I.** American College of Physicians and UCLA at UCLA. Saturday-Sunday. 12 hrs. $160. Contact: UCLA.

December 8—**Chronic Diarrhea—Its Diagnosis and Treatment.** LLU. Wednesday. 4 hrs.

December 9-10—**MKSAP Review Course.** American College of Physicians and UCD at Hyatt Union Square, San Francisco. Thursday-Friday. 12 hrs. Contact: UCD.

January 6-7—**American College of Physicians—Regional Meeting.** Ala Moana Americana Hotel, Honolulu. Thursday-Friday. Contact: Robert A. Nordyke, MD, 2013 Kakela Dr., Honolulu 96822.

January 10-14—**7th Annual Echocardiography Conference.** Honolulu Medical Group at Westin Wailea Hotel, Maui. Monday-Friday. 30 hrs. $495. Contact: Yvonne Brewer, Honolulu Med. Grp., Research and Education Fndn., 550 S. Beretania St., Honolulu 96813. (808) 537-2211.

January 12—**12th Annual Gastroenterology Symposium.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

January 14-15—**Third Clinical Conference on Congenital Heart Disease.** Childrens Hospital at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Bernard L. Tucker, MD, 1136 W. 6th St., Los Angeles 90017. (213) 482-3121.

January 22-29—**Advanced Problems in Cardiac Emergencies.** See Emergency Medicine, January 22-29.

January 26—**Biannual Stroke Symposium.** American Heart Assn., Santa Clara Co. Chap., at Le Baron Hotel, San Jose. Wednesday. Contact: Harriet M. Schutte, AHA, 3003 Moorpark Ave., San Jose 95128. (408) 247-8555.

February 9—**Cardiology Symposium on Pacemakers.** N. T. Enloe Memorial Hospital, Chico. Wednesday. 6 hrs. $50. Contact: Cont. Ed. Office, N. T. Enloe Mem. Hosp., W. 5th Ave. and The Esplanade, Chico 95926. (916) 891-7375.

February 9—**Common Skin Diseases.** LLU. Wednesday. 4 hrs.

February 9-11—**Recent Advances in Neurology.** UCSF at Fairmont, San Francisco. Wednesday-Friday. 15 hrs. $250.

February 11-13—**Pathophysiology and Techniques of Cardiopulmonary Bypass: III.** Cardiothoracic Research and Education Foundation at Hilton Beach and Tennis Resort, San Diego. Friday-Sunday. Contact: CREF, P.O. Box 33185, San Diego 92103. (714) 272-3126.

February 15-18—**Clinical Hematology and Oncology: 1983.**

(Continued on Page 26)

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Scripps Clinic and Research Foundation at Sheraton Harbor Island, San Diego. Tuesday-Friday. 31 hrs. $390. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 17-19—**Therapeutic and Diagnostic Uses of the Cardiac Catheter.** American College of Cardiology at Bonaventure Hotel, Los Angeles. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

February 21-23—**Recent Advances in Clinical Endocrinology.** UCSF at Sir Francis Drake Hotel, San Francisco. Monday-Wednesday.

February 26-27—**Immunology.** STAN. Saturday-Sunday. 13 hrs. $250.

February 26-27—**Basic Neuroscience.** STAN. Saturday-Sunday. 11 hrs. $250.

February 27-March 2—**Basic Cardiology for the Practicing Physician.** UCSF at Hyatt, Lake Tahoe. Sunday-Wednesday. 15 hrs. $200.

March 4—**9th Annual Diabetes Conference.** UCD at Sacramento. Friday. 7 hrs.

March 6-8—**Dermatology Consultants' Course.** UCSF at Yosemite. Sunday-Tuesday.

March 9—**Therapy of Ischemic Heart Disease.** LLU. Wednesday.

March 10-11—**Neurosciences Symposium III.** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Friday-Saturday. 14 hrs. Contact: Janette Wackerly, Sutter Gen. Hosp., 2820 L St., Sacramento 95816. (916) 454-2222, ext. 1430.

March 14-15—**MKSAP Review Course.** American College of Physicians and UCD at Hyatt Union Square, San Francisco. Monday-Tuesday. 12 hrs. Contact: UCD.

March 14-18—**Allergy and Dermatology.** Symposium Maui, Inc.; American Academy of Family Physicians, Hawaii Chap.; Hawaii Medical Assn. at Royal Lahaina Resort, Kaanapali, Maui. Monday-Friday. 22 hrs. Contact: Joe Harrison, MD, Symposium Maui, Inc., P.O. Box 10185, Lahaina, Maui 96761.

March 19-20—**MKSAP VI Review Course—Internal Medicine Review Part II.** American College of Physicians and UCLA at UCLA. Saturday-Sunday. 12 hours. $160. Contact: UCLA.

March 26-April 2—**Vascular Disease.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

OBSTETRICS AND GYNECOLOGY

December 10-12—**Current Issues in Perinatal Medicine.** Memorial Hospital Medical Center-UCI Center for Health Education at Marriott's Rancho Las Palmas Resort, Rancho Mirage. Friday-Sunday. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 29—**Ovulation Update: 1983.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. $75. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 5-11—**Perinatal Medicine.** USC at Royal Lahaina, Maui. One week. 23 hrs. $425.

February 6-11—**OB/GYN Update.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 22 hrs.

February 14-18—**38th Annual Postgraduate Assembly.** OB-GYN Assembly of So. Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 12-19—**Office Gynecology.** Univ. of Washington School of Medicine at Sheraton Waikoloa, Kona. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

March 20-23—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

PEDIATRICS

November 19-22—**Pediatric Update.** Calif. Chapters 1, 2, 3, American Academy of Pediatrics, at Hilton, Las Vegas. Friday-Monday. 14 hrs. $195, members; $220, nonmembers. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

November 28-30—**Kids Have Bones, Too.** UCD at Hyatt Del Monte, Monterey. Sunday-Tuesday. 14 hrs. $165.

December 4—**Emergency Pediatrics, Part II.** Calif. Chapters, American Academy of Pediatrics, at Holiday Inn on Union Square, San Francisco. Saturday. Contact: Beverly Busher, No. Calif. Chap., AAP, 422 Alexander Ave., Larkspur 94939. (415) 924-9613.

January 12—**22nd Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday. 4½ hrs. Contact: Eve Black, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

January 31-February 3—**8th Annual Winter Ski and Study Symposium.** Calif. Chapters 1 and 2, American Academy of Pediatrics, at Caesar's, Lake Tahoe. Monday-Thursday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

February 17-19—**Pediatric Urology.** See Surgery, February 17-19.

February 23-March 1—**Adolescent/Young Adult Medicine.** Hurley Medical Center at Wailea Beach Hotel, Maui. One week. 20 hrs. Contact: Hurley Med Ctr., Dept. of Cont. Med. Ed., One Hurley Plaza, Flint, MI 48504. (313) 766-0142.

March 10-13—**Combined Southern California Pediatric Postgraduate Meeting.** Calif. Chap. 2, American Academy of Pediatrics, at Hilton Riviera, Palm Springs. Thursday-Sunday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

March 19-26—**Updates in Pediatrics: An Epic Medical Expedition.** American Institute of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

PSYCHIATRY

November 20-27—**3 for 1: Protology; Psychiatry; Principles.** Univ. of Washington School of Medicine at Sheraton Waikoloa, Kona. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

December 9-12—**New Approaches in Psychoanalytic Therapy.** American Academy of Psychoanalysis at Hotel del Coronado, Coronado. Thursday-Sunday. 20 hrs. Contact: Vivian Mendelsohn, AAP, 30 E. 40th St., Suite 608, New York 10016. (212) 679-4105.

January 3-7—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 9-13—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 17-21—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $155. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

January 23-28—**9th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 26 hrs. $265.

January 29—**Heinz Von Foerster on Applications of the Constructivist Perspective in Family Therapy.** Mental Research

(Continued on Page 33)

From the Chairman of the Board

"Because Blue Shield Physician Membership will soon be more meaningful than ever before, I am taking this opportunity to urge you to join the more than 28,000 physicians throughout the state. No other health care financing organization in the state, today or any time over the 43-year history of Blue Shield, has demonstrated such a concern for its members, whether they be physicians or subscribers."

–A recent letter from Robert W. Walker, Chairman of the Board, Blue Shield of California, to California Physicians.

Join the over 28,000 Blue Shield Physician Members who are already getting prompt, fair payment directly from Blue Shield for almost 1,500,000 subscribers.

The new Preferred Provider Plan will still allow these subscribers to choose their physicians, but will pay non-member providers at a lesser rate than the usual, customary payment to Preferred Providers.

Find out more today about the fee-for-service plan that's fair for everyone. For more information call Blue Shield Professional Relations, (415) 445-5211 or (213) 642-5822, or RSVP by sending your business card to Professional Relations, Box 7136, San Francisco, CA 94120.

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CAN YOUR LIABILITY COVERAGE HANDLE A STRESS TEST?

Take a close look at your malpractice insurance and you may find it's in weaker condition than you realized.

With lawsuits increasing and awards rising, insurance companies are under pressure. This often affects rates, reduces coverage and shifts pressure to you.

Reduced coverage creates several points of stress. For example, you could lose your settlement rights in a suit. Though some companies promise settlement rights, they may limit your coverage to the amount of a settlement offer. And if you want to go ahead and fight for your good name, losing means that a greater award is yours to pay. And pay.

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(Continued from Page 26)

Institute, Palo Alto. Saturday. 6 hrs. $85. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 3-6—**Cognitive, Emotional and Neurophysiologic Effects of Head Trauma: Post-Concussion Syndrome.** So. Calif. Neuropsychiatric Institute at La Quinta Hotel, La Quinta. Thursday-Sunday. 15 hrs. Contact: Gail Waldron, MD, SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (714) 454-2102.

February 26-27—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 11 hrs. $250.

RADIOLOGY AND PATHOLOGY

December 2-4—**International Symposium on Medical Virology.** UCI at Disneyland Hotel, Anaheim. Thursday-Saturday. 23 hrs. Contact: Luis M. de la Maza, MD, PhD, Dept. of Pathology, UCI Med. Ctr., Orange 92668. (714) 634-6868.

December 5-7—**Leucocyte Conference.** USC at Asilomar, Pacific Grove. Sunday-Tuesday.

January 10-13—**Imaging Symposium.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, Coronado. Monday-Thursday. 27 hrs. $350. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

January 17-21—**Advanced Microbiology: Recent Developments and New Frontiers.** American Society of Clinical Pathologists at Holiday Inn-Fisherman's Wharf, San Francisco. Monday-Friday. 32 hrs. $600/$700. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

January 17-21—**Interventional Radiology and Diagnostic Imaging Modalities.** UCSF at Fairmont, San Francisco. Monday-Friday. 33 hrs. $400.

January 22-30—**11th Annual Diagnostic Radiology Seminars.** UCSF at Waiohai Hotel, Kauai. One week. 31 hrs. $350.

January 24-27—**Chest Radiology 1983.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Thursday. 24 hrs. $300. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

February 2-4—**5th Annual Immunoassay Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 21 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (714) 455-9100.

February 2-4—**10th Annual Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 23 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

February 2-7—**Society of Nuclear Medicine—2nd Conjoint Winter Congress.** Cathedral Hill Hotel, San Francisco. Wednesday-Monday. Contact: SNM, Meetings Dept., 475 Park Ave. So., New York 10016. (212) 889-0717.

February 4-6—**35th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. $125, members; $175, nonmembers. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 6-11—**5th Annual Winter Conference in the High Sierra—OB/GYN Imaging.** American College of Medical Imaging at Sahara, Lake Tahoe. Sunday-Friday. 25 hrs. $347, members; $385, nonmembers. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 6-12—**Los Angeles Radiological Society—Annual Post Convention Seminar.** Hyatt Regency, Kaanapau, Maui. One week. 20 hrs. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 9-12—**Nuclear Radiology.** UCSD at Hotel del Coronado, Coronado. Wednesday-Saturday. 20 hrs. $335. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

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February 23-25—**New Imaging Modalities in Radiology.** Memorial Hospital Medical Center at Hilton Riviera, Palm Springs. Wednesday-Friday. 18 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

March 9-11—**Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at North Lake Tahoe. Wednesday-Friday. 18 hrs. $280. Contact: Arthur B. Dublin, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 14-18—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $400.

March 14-18—**4th Midwinter Diagnostic Radiology Conference on Imaging Modalities in the Chest and Abdomen.** Loyola Univ. at Kapalua Bay Hotel, Maui. Monday-Friday. 20 hrs. $325. Contact: L. Gunzburger, PhD, Div. of Cont. Med. Ed., Loyola Univ. Med. Ctr., 2160 S. 1st Ave., Maywood, IL 60153. (312) 531-3236.

March 21-25—**Obstetric and Gynecologic Pathology.** American Society of Clinical Pathologists at San Diego. Monday-Friday. 28 hrs. $550/$650. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

March 23-25—**Current Concepts in Surgical Pathology.** STAN. Wednesday-Friday. 21 hrs. $400.

SURGERY

November 18-21—**Modern Concepts in Operative Neurosurgery, Critical Care and Rehabilitation.** Comprehensive Central Nervous System Injury Fndn. and Inst. for Medical Education and Research at Hilton on Mission Bay, San Diego. Friday-Sunday. 20 hrs. $250. Contact: CNS Injury Fndn., P.O. Box 9494, San Diego 92109. (714) 272-3126.

November 28-December 10—**Temporal Bone Surgical Dissection Course.** House Ear Institute, Los Angeles. Two weeks. 100 hrs. $1,500. Contact: Antonio De La Cruz, MD, House Ear Inst., 256 S. Lake St., Los Angeles 90057.

December 3-4—**The Anterior Cruciate Ligament "State of the Art."** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 16 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

December 4—**Photocoagulation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $250. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

January 12—**Office Urology.** LLU. Wednesday. 4 hrs.

January 14-15—**10th Annual Santa Clara County Surgical Seminar—Critical Care and Current Concepts.** Santa Clara Co. Surgical Seminar Assn., at Le Baron Hotel, San Jose. Friday-Saturday. 15 hrs. $160. Contact: Surgical Seminar, c/o Kenneth Watanabe, MD, 150 N. Jackson Ave., #209, San Jose 95116.

January 17-19—**Society of Thoracic Surgeons.** Hilton, San Francisco. Monday-Wednesday. Contact: STS, 111 E. Wacker Dr., Chicago 60601.

January 21-22—**5th Annual Postgraduate Course on Surgery.** UCD at Holiday Inn, Sacramento. Friday-Saturday. 14 hrs. $135.

January 24-26—**Midwinter Clinical Conference in Ophthalmology and Otolaryngology.** Research Study Club at Hilton, Los Angeles. Monday-Wednesday. 21 hrs. $200. Contact: Research Study Club, P.O. Box 49412, Los Angeles 90049.

January 29—**Practical Use of the Visual Physiology Laboratory.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $50. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 3-5—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 6-10—**Lake Tahoe Vitreo-Retinal Symposium.** Retina Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

February 14-17—**Musculo-Skeletal Disease—New Diagnostic Concepts and Modalities.** UCSD at Hotel del Coronado, Coronado. Monday-Thursday. 21 hrs. $300. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

February 17-19—**Pediatric Urology.** American Urological Assn. at Hilton, San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, P.O. Box 25147, Houston TX 77265. (713) 790-6070.

February 19-26—**Updates in Trauma: An Epic Medical Expedition.** American Inst. of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

February 23-24—**Neurological Problems.** Federation of Western Neurological Societies and UCLA at UCLA. Wednesday-Thursday. Contact: UCLA.

February 25-26—**Ophthalmology Update on Basic Sciences for the Clinician.** Update: Fndn. for Systematic Postgraduate Education in Ophthalmology, UCD, PMC, UCSF, STAN at San Franciscan Hotel, San Francisco. Saturday-Sunday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2763.

March 7-11—**Surgical Forum.** Soc. of Graduate Surgeons of the Los Angeles Co./USC Med. Ctr. at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Soc. of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 9-10—**American Orthopaedic Foot Society.** Anaheim. Wednesday-Thursday. 12½ hrs. Contact: Kenneth A. Johnson, MD, Dept. of Orthopedics, Mayo Clinic, Rochester, MN 55905. (507) 284-2778.

March 10-15—**American Academy of Orthopaedic Surgeons.** Convention Center, Anaheim. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 14-18—**Sports Medicine.** Univ. of Hawaii at Princess Kaiulani Hotel. Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 17-19—**Gynecologic Surgery With Emphasis on Gynecologic Urology.** Memorial Hospital Medical Ctr. at Hilton Riviera, Palm Springs. Thursday-Saturday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

March 19-20—**Ophthalmology Update on Basic Sciences for the Clinician.** Update: Fndn. for Systematic Postgraduate Education in Ophthalmology, UCD, PMC, UCSF, STAN at San Franciscan Hotel, San Francisco. Saturday-Sunday. Contact: Update, 3910 San Hill Rd., Woodside 94062. (415) 563-4321, ext. 2763.

March 19-23—**20th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Saturday-Wednesday.

March 23-25—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt, Palo Alto. Wednesday-Friday. 16 hrs. $225.

March 24-27—**11th Annual Symposium on Vascular Surgery.** UCLA at Palm Springs. Thursday-Sunday.

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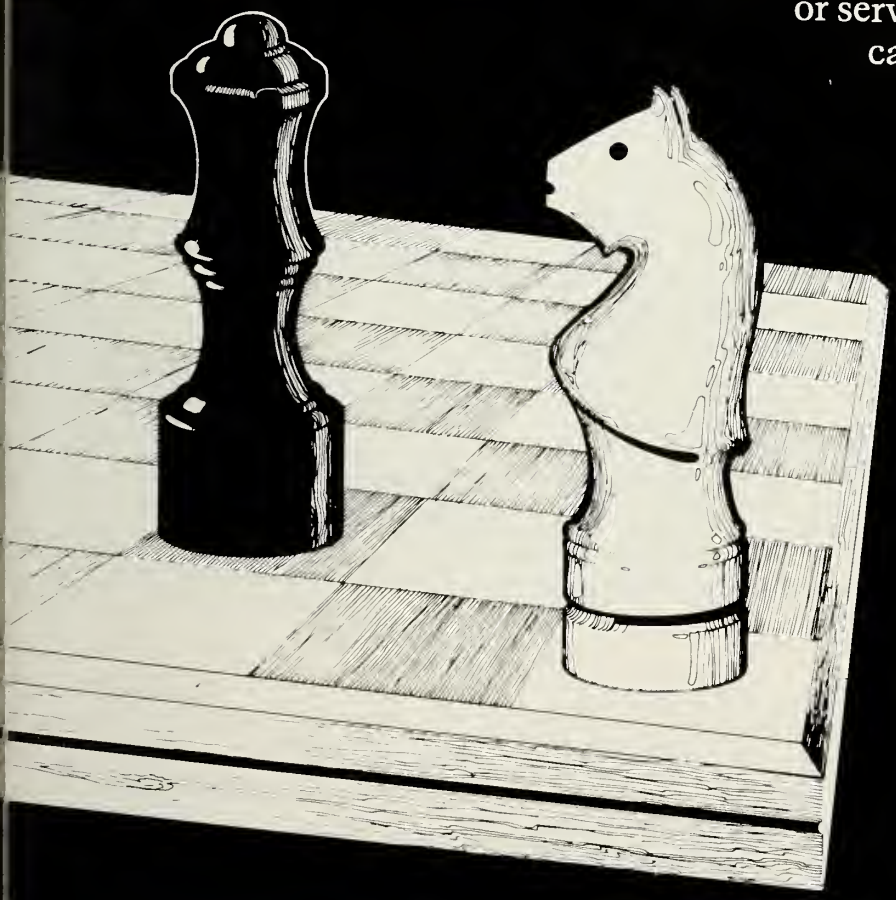

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Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide, dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Campylobacter *Enteritis: A Large Outbreak Traced to Commercial Raw Milk*

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From April 24 to May 11, 1981, an outbreak of approximately 200 cases of Campylobacter jejuni *enteritis occurred in Arizona in persons who drank one brand of unpasteurized milk. Two cohort studies showed that households with members who drank raw milk reported diarrheal illness significantly more frequently than those in which no one drank raw milk (*P=.003 *and* P=.001*; relative risk 4.70 and 3.85, respectively). Of 19 serotyped* C jejuni *organisms isolated from persons who drank raw milk from the implicated dairy, 18 were of a single serotype.*

C jejuni *was not detected in the milk or the milk filters cultured a week after the outbreak, but fecal excretion of* Campylobacter *of multiple serotypes was higher in the dairy herd that produced the implicated raw milk (48 percent) than in control herds (16 percent).*

In Great Britain unpasteurized (raw) milk has been described as the major vehicle of transmission in human outbreaks of enteritis caused by *Campylobacter jejuni*.[1] In the United States, cases associated with raw milk ingestion have been reported from California[2] and Colorado.[3] In the past few years it has become apparent that *C jejuni* is an important cause of diarrheal disease and that with appropriate laboratory techniques this pathogen can be readily isolated from fecal specimens. The appropriate methods include a microaerophilic atmosphere, incubation at 42°C (107°F) and a selective medium. Methods to accomplish these growth requirements have recently become commercially available, and many microbiologic laboratories in the United States are now capable of isolating this organism. As a result, in 1981 three outbreaks of *Campylobacter* enteritis that involved consumers of commercially available raw milk were reported to the Centers for Disease Control (CDC) from Oregon (50 cases),[4] Kansas (more than 100 cases)[5] and Arizona (nearly 200 cases). This report describes the Arizona outbreak

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and shows the usefulness of *Campylobacter* serotyping in the investigation of such outbreaks.

Methods

Epidemiologic Investigation

On May 4, 1981, a physician reported to the Pima County (Arizona) Health Department that an 82-year-old woman admitted to hospital in Tucson with bacteremia and enteritis due to *C jejuni* habitually drank five glasses of raw milk a day. To locate additional recent cases of diarrheal disease, the health department contacted physicians in the Tucson area who were likely to see patients with an acute gastrointestinal illness and all hospital epidemiologists and laboratories in Tucson. In this way, 39 cases were found. A case was defined as diarrhea (three or more loose stools per day for more than one day) or two of four other enteric symptoms (bloody diarrhea, fever, abdominal pain or vomiting) in a person who drank raw milk from dairy A in the week before onset of illness. On May 8 a public announcement was made that notified the community of a possible outbreak of enteritis and asked that persons with a current or recent gastrointestinal illness call the health department. Persons who called were questioned about demographic data; personal and family histories of diarrheal disease; recent consumption of raw milk, untreated water or poorly cooked meats, and whether they had had contact with ill or well pets and other domestic or wild animals. Persons with an illness suggesting *Campylobacter* enteritis were asked to submit a stool specimen to their physician or to the health department.

To determine whether those who drank raw milk had more enteritis from late April to early May than those who did not drink raw milk, we interviewed two groups of persons known to include many raw milk drinkers. The first group were members of a cooperative grocery store (COOP) and the second were recent patients of a chiropractor who advocated raw milk ingestion for many of his patients and who also owned a chain of health food stores in Tucson. The COOP and the health food stores sold both pasteurized and unpasteurized milk. We obtained names and telephone numbers of active COOP members from weekly work assignment rosters used at the store and randomly selected every fifth household from the weekly rosters for the previous three months. Similarly, from the chiropractor we randomly selected every fifth name from a roster of patients seen for the first time during the three months before the outbreak. On May 10 we conducted a telephone survey of 106 households that belonged to the COOP and 95 households of patients seen by the chiropractor. About 80 percent of the originally selected households were successfully reached. We did not encounter an overlap between these two groups, but some of the households that we surveyed had already reported illness to the health department. Each household was asked what brand of milk they drank and the age, sex, milk consumption and illness history during the last two weeks for each member of the family. The cohort studies were analyzed by a two-tailed Fisher's exact test.

Laboratory Investigation

Rectal swabs or fecal specimens from humans were transported on Cary-Blair medium to the Arizona Department of Health Services laboratory or the Enteric Diseases Branch laboratory, CDC, for isolation of *C jejuni* by methods already described.[6] Rectal swabs were taken from cattle at the implicated dairy and from cattle from three nearby dairy herds (dairies B, C and D). These specimens were cultured for *Campylobacter* by the Arizona Department of Health Services laboratory. Human and animal *Campylobacter* isolates were transported to CDC on Wang's medium.[7] Serotyping was done at CDC by the method of Penner and Hennessy.[8]

A total of 16 milk samples from containers with pull dates indicating that the milk was on sale during the outbreak were first plated directly onto Campy-BAP medium and were also filtered through a 0.65 μm filter (Millipore Corporation), and the filtrate was plated onto Campy-BAP. The milk and filtrates were inoculated into two enrichment broths (Oosterom's medium and Bryner's medium). The enrichment broths were incubated for 24 hours at 42°C and then subcultured to Campy-BAP. Sections of four milk filters used on May 8, 9 and 10 to filter milk from the implicated herd were placed into 250 ml of a bile-containing enrichment medium (Oosterom's). They were incubated for 24 hours at 42°C and then subcultured from enrichment medium to Campy-BAP.

Results

Outbreak Investigation

Using the case definition outlined earlier, we identified 190 cases in 88 families distributed

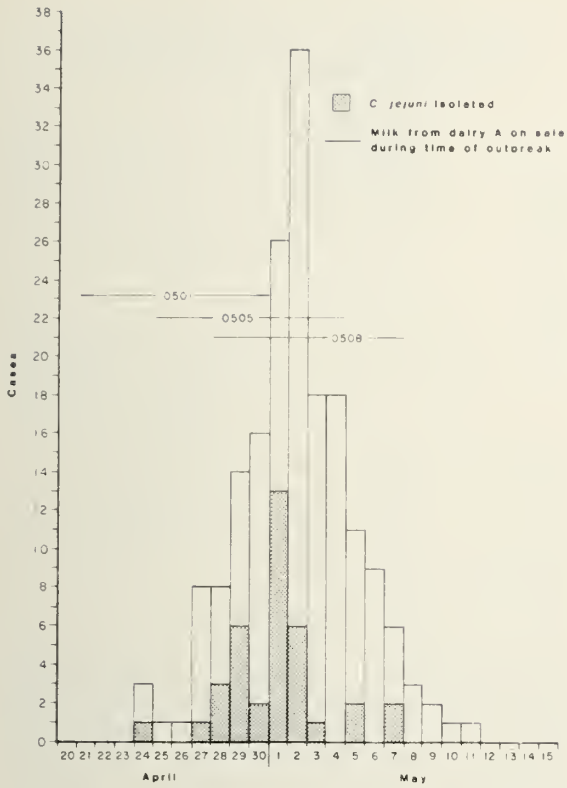

Figure 1.—Cases of enteritis associated with raw milk, Tucson, Arizona, April 20 through May 15, 1981.

C jejuni = Campylobacter jejuni

throughout Tucson and Pima County. Single rectal swabs were obtained from 58 of these ill persons, and *C jejuni* was isolated from 37 (64 percent). About half of the ill persons were male, and the median age was 23 (range, 6 months to 85 years). The highest attack rate in drinkers of dairy A milk in the affected families occurred in persons 20 to 29 years old (40 [95 percent] reported illness) and the lowest attack rate occurred in adults 40 years old or older (33 [63 percent] reported illness).

In the 88 families, 190 (79 percent) of 241 persons who drank raw milk from dairy A but none of the 77 persons who did not drink raw milk became ill with an illness having all the features of *Campylobacter* infection. In the group that drank raw milk, 70 percent of 57 persons who drank less than a glass of milk, 86 percent of 70 who drank one to two glasses and 82 percent of 91 who drank more than two glasses per day reported illness (23 unknown). The difference between drinking less than one glass and drinking one or more glasses was significant ($P = .03$), but the linear trend was not.

Those who met the case definition reported the following symptoms: diarrhea (90 percent), abdominal pain (84 percent), fever (69 percent), headache (69 percent), nausea (64 percent), bloody diarrhea (29 percent) and vomiting (20 percent). Onsets of illness occurred between April 24 and May 11 and peaked on May 1 and 2 (Figure 1). Voluntary pasteurization of milk from dairy A began on May 8.

Besides the index case, the only other person known to have been admitted to hospital was a 22-year-old man who a year earlier had had a splenectomy following trauma. This otherwise healthy young man drank one glass of milk three days before an illness characterized by high fever followed by explosive diarrhea. Cultures of blood and stool specimens done soon after hospital admission grew *C jejuni*. He recovered quickly after a short course of intravenously given fluids and antibiotics.

Illness was also reported in seven families in Mesa, a small town near the dairy, where the raw milk was also distributed. In these families 18 persons ranging in age from 1 to 76 years met the case definition. The peak date of onset of symptoms in this group was May 3. *C jejuni* was isolated from two of five rectal swabs taken from ill persons.

In the COOP survey, 6 of 12 households in which raw milk from dairy A was drunk reported one or more household members with diarrheal illness, while only 10 (11 percent) of 94 households in which raw milk from dairy A was not drunk reported illness ($P = .003$, relative risk = 4.7 [95 percent confidence interval (CI) between 1.79 and 12.33]). Similarly in the health food survey, 9 of 18 households in which raw milk was drunk reported one or more household members with diarrheal illness, while 10 (13 percent) of 77 households who did not drink raw milk reported illness ($P = .001$, relative risk = 3.85 [95 percent CI between 1.68 and 8.81]).

Investigation of the Dairy

Dairy A has been in operation for more than 20 years. At the time of the investigation the dairy was milking 200 cows and producing about 10,000 gal of milk a week. Of the 10,000 gal, 7,000 gal are pasteurized and distributed in Phoenix and 3,000 gal are not pasteurized, of which 2,000 gal are distributed in Tucson and the rest in the area around the dairy. The health food chain buys an estimated 1,000 gal a week

(200 gal per store) and the COOP grocery buys about 120 gal a week. Raw milk going to Tucson is produced on Friday and Monday and shipped on the following days. The raw milk that was on the shelves during the outbreak was distributed on April 21, 25 and 28. Milk is dated ten days after delivery; therefore, the milk delivered on April 21 was labeled "0501," milk delivered on April 25 "0505" and milk delivered April 28 "0508." Discussions with the dairyman indicated that there had been no changes in his dairy practices and there had not been an increase in mastitis or enteritis in his milking herd.

Laboratory Investigation

Campylobacter was not isolated from ten milk specimens obtained from the homes of ill persons and from the stores with milk on the shelf with the suspected pull dates, nor was *Campylobacter* found on cultures from five milk filters obtained on May 8, 9 and 10 from dairy A.

A sample of 42 healthy cattle from dairy A and 50 cattle each from three nearby dairy herds was tested for fecal excretion of *C jejuni*. *Campylobacter* was isolated from 20 (48 percent) of 42 cows at dairy A and from 22 percent, 16 percent and 12 percent of the cows sampled at the other three dairies.

Of 19 *C jejuni* isolates from persons who drank raw milk from the implicated dairy, 18 (95 percent) were one serotype (PEN-2), but multiple serotypes were isolated from the dairy herds. In the sample from the implicated herd, PEN-7 was the predominant serotype, whereas PEN-2 was not recovered (Table 1).

TABLE 1.—Campylobacter *Isolations and Serotypes From Feces From Humans and Cows in a Raw Milk-Associated Outbreak in Arizona, April Through May 1981*

Source	Campylobacter Isolation: No. Tested	Campylobacter Isolation: No. Positive	Serotypes*: No. Tested	Serotypes*: Serotype (No. Positive)
Human				
Tucson	58	37	17	2(16), 19 (1)
Mesa	5	2	2	2(2)
Cattle				
Dairy A	42	20	20	7(11), 16/13(2) 16(2), 37(1), 4(1) 7/36(1), (2 untypeable)
Dairy B	50	11	3	11(3)
Dairy C	50	8	7	1/8(2), 7/4(1), 7(2), 7/25(1), 2(1)
Dairy D	50	6	2	11(1), 7(1)

*Described in Penner and Hennessy.[8]

Discussion

Because *C jejuni* is harbored by a large and diverse group of animals, human infection may be acquired from many sources. Animals with which man has frequent contact such as dogs, cats, poultry, cattle, sheep and swine can all excrete this organism.[9] Studies in zoos and of trapped wild animals have indicated a high rate of fecal carriage among migratory waterfowl[10] and hoofed wild animals.[11] Transmission from pets has occurred during contact with these animals.[12] Transmission from other domestic animals occurs indirectly through consuming inadequately cooked meats or unpasteurized dairy products. Outbreaks or cases have been noted to occur after drinking raw milk as in this outbreak, and after eating raw chicken,[13] hamburger,[14] clams and processed turkey. Infection can also occur after drinking contaminated water. Large waterborne outbreaks have been caused by unchlorinated or inadequately chlorinated municipal water systems,[15] and sporadic cases have been traced to drinking untreated surface water.[16]

Foods with high fat content such as milk, cheese, chocolate and hamburger are especially efficient vehicles for the transmission of *Salmonella*[17]; this type of vehicle may be just as important in the transmission of *Campylobacter*. Two volunteers became ill after ingesting *C jejuni* in milk; one volunteer became ill after ingesting only 500 organisms.[18]

Because we lack sensitive techniques for isolating *Campylobacter* from milk, we do not know how often or to what degree commercial milk is contaminated before it is pasteurized. Milk is probably contaminated from cow feces at the time of milking, but bovine mastitis is another possible source of contamination.[19]

Investigation at the implicated dairy did not disclose improper milking techniques or dairy practices. Fecal contamination cannot be totally eliminated even by meticulous dairy hygiene practices, and *C jejuni* can survive for weeks in milk kept at 4°C (39.2°F),[20] so pasteurization appears to be the only way to completely eliminate the risk of milk-borne *Campylobacter* disease. In England and Wales many milk-borne outbreaks have occurred as a result of faulty pasteurization, while the outbreaks in the United States have

occurred because of people's insistence on drinking unpasteurized milk. The increase in the number of milk-borne disease outbreaks due to *Campylobacter* appears to be the result of increased surveillance and awareness of the epidemiology of *Campylobacter,* though an increase in the consumption of raw milk in the United States may be a contributing factor.

Since the outbreak had begun to wane before pasteurization or public notification occurred, other factors must have initiated its decline. The outbreak may have been limited in part by the exhaustion of susceptible persons among those who drank raw milk. At the time of the investigation only 1,100 gal of raw milk were sold per week in Tucson. From the survey data we know that raw milk drinkers usually bought the same brand of milk each week, and that they consumed an average of ½ gal per week. We found little difference in attack rates between those who said they drank large quantities and those who drank small quantities. The absence of a pronounced dose effect supports Robinson's theory that a small dose in milk can cause illness.[18] Another factor that may have contributed to the end of the outbreak is that the milk in subsequent deliveries may have been less heavily contaminated.

Serotyping identified a common strain in humans and supported the epidemiologic evidence that the cases of *Campylobacter* enteritis that occurred in two separate locations in Arizona were derived from a single source. The epidemic strain may have been missed in the sampling of the implicated dairy herd because it came from a single cow from which specimens were not cultured, the infection was transient and no longer present when the cultures were done or the epidemic strain may not have been present in feces at all but derived from another source such as mastitis. Further work is necessary to determine how *Campylobacter* is introduced into a dairy herd and then contaminates milk.

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Middle Ear Effusion in Children: A Report of Treatment in 500 Cases

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Records were studied of 500 children younger than 9 years of age with middle ear effusion who had received one of three treatment strategies: (1) administration of medication, including decongestants, antihistamines or antibiotics (or a combination), (2) administration of medication for a limited time and then surgical therapy if effusion did not resolve or (3) myringotomy done immediately with insertion of ventilation tubes and, in some cases, removal of adenoids.

Early surgical intervention resulted in significantly shorter delay in hearing restoration. It did not result in a lower recurrence rate and it did not reduce the number of occasions when thick fluid, as compared with thin fluid, was found at operation. Four children for whom medical and surgical treatment failed were considered candidates for mild gain, low maximum-power-output hearing aids. All other children had normal hearing after treatment. Medication was successful in achieving this goal in 48 percent of the cases.

THE EFFECTIVENESS of treatment for middle ear effusion has recently come under scrutiny as delay in resolution of associated mild fluctuating hearing loss can often be as great as three years. These years are usually during the critical language learning period.

In this paper we review the effectiveness of three treatment strategies used by physicians of the Otologic Medical Group, Inc., Los Angeles, in 500 children to minimize delay in resolution of effusion. We also examine how many children there were in this group in whom medical treatment failed and who therefore must be considered candidates for hearing amplification.

From the Otologic Medical Group, Inc., and supported by funds from the House Ear Institute, Los Angeles.

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Review of the Literature

Professionals involved with delayed speech and language development have become increasingly concerned about the deleterious effects of ongoing mild conductive hearing loss due to middle ear effusion. Mild conductive hearing loss is known to significantly delay speech and language, causing subsequent reduction in academic achievement.[1] Otologists and pediatricians are also concerned about the occasional sequelae of unresolved otitis media, including coalescing mastoiditis, central perforation, and primary and secondary acquired cholesteatomas. These effects of unresolved effusion have prompted physicians to seek to minimize delay in resolving the problem.

Although there is agreement that delay should be minimized, there is no agreement in the litera-

ture as to which treatment most effectively achieves this goal. Baron[2] recommended treatment with antimicrobial agents and, when warranted, myringotomy. Until recently Bluestone and Shurin[3] agreed. In a recent article,[4] however, Bluestone reversed his position and now recommends decongestant and antihistamine administration. Expressing a slightly different point of view, Sadé[5] states that antimicrobial therapy is of no value and may even be contraindicated; he recommends surgical ventilation. Harell and Shea[5] warn against the overuse of ventilation tubes and state that myringotomy and autoinflation associated with medical treatment are at least as effective as ventilation tubes, and may be superior.

Even after the infection in otitis media has resolved, however, effusion in the middle ear space may persist. Delay in spontaneous resolution of the fluid may be as long as six months. Additionally, many children younger than 6 years of age face repeated episodes of effusion. Some audiologists and otologists are now suggesting that children with recurrent middle ear effusion should be considered candidates for very low gain hearing aids with low maximum-power output.[7]

Materials and Methods

Histories were reviewed for 500 patients younger than 9 years of age with middle ear effusion who were seen by the Otologic Medical Group. All who were included in the present study were subsequently diagnosed as having chronic serous otitis media. Not included in this study were children who have sensorineural hearing loss, acute serous otitis media, history of mastoiditis or cholesteatoma, or cleft palate or submucous cleft of the hard palate.

This study was retrospective by design. None of the physicians involved in treating young children as part of the Otologic Medical Group were willing, for the sake of research, to place young children on a treatment regimen that they thought would not be successful.

The following information was extracted from each treatment history:

- Factors affecting choice of treatment, such as a previous surgical procedure for middle ear effusion, duration of hearing loss, and pure-tone air and bone conduction thresholds before treatment.
- Dimensions of effectiveness of treatment, including the amount of delay in resolution of hearing loss, whether or not there was recurrence of effusion, viscosity of fluid found at operation, and specific medications recommended and their relative effectiveness.

Depending on the duration of the problem, degree of hearing loss and the age of the patient, Otologic Medical Group physicians either prescribed medications for a monitored period or scheduled a myringotomy and possible adenoidectomy to be done as soon as possible. Based on their professional experience, the physicians prescribed different medications: some used antibiotics, antihistamines and decongestants in combination; others used antibiotics alone or decongestants and antihistamines in combination without antibiotics.

In all cases of myringotomy, collar-button or mesh-type tubes were placed in the tympanic membrane. Collar-button tubes were always tried initially rather than mesh tubes because removal of the latter requires a second surgical procedure. By ventilating the middle ear with a collar-button tube, it is hoped that edema and hyperplasia of the mucosa will subside by the time the tube is extruded and that effusion will not recur. Mesh tubes were used after collar-button tubes had been extruded and effusion recurred or when there was evidence of impending permanent damage to the tympanic membrane. This evidence included epitympanic retraction pockets, monomeric membranes, tympanosclerosis or partially atelectatic membranes.

Adenoidectomy was also carried out in about 20 percent of the cases.

Results

The factors affecting a physician's choice of treatment were the duration of loss and a prior surgical procedure for middle ear effusion. Duration was on the average 17.1 months for the children who initially had a surgical procedure and 10.5 months for the children who were initially treated medically. Similarly, three times as many children in the former group (27 percent) than in the medically treated group (9 percent) had undergone a previous surgical procedure. A longer duration of middle ear effusion or a history of a previous operation both prompted early surgical intervention.

Two factors that affected treatment choice less were degree of hearing loss and academic performance. A slightly higher percentage of children in the initially surgically treated group (35 per-

cent) than in the medically treated group (27 percent) were reported to be doing poorly in school or to have delayed speech and language development. For degree of loss the pattern was essentially the same in both groups: 67 percent of the initially medically treated and 70 percent of the initially surgically treated groups had pure-tone air conduction thresholds greater than a 25 dB hearing threshold level for 250 to 4,000 Hz. These findings are summarized in Table 1.

Effectiveness of Treatment

After treatment all but four children had pure-tone air conduction thresholds of 15 dB or better for 250 to 4,000 Hz in both ears. For the exceptions, even repeated insertions of temporary or permanent ventilation tubes were unsuccessful in remedying the problem. These children were eventually fitted with mild gain, low maximum-power-output hearing aids. Except for these four cases, surgical intervention was always successful in restoring hearing. Treatment with medication was successful 48 percent of the time. Children for whom medication was not successful later underwent a surgical procedure.

Several dimensions of treatment effectiveness were examined. Delay in restoration of hearing was notably different for the three treatment strategies. Mean delay for the initially medically treated group was 4.8 months; 3.4 months for children who had medication first, then a surgical procedure, and 1.6 months for the group who had surgical intervention first (Table 2).

Though the medication-first strategy caused longer delay, it did not adversely affect the recurrence rate. If medication was successful, a child was no more likely to have recurrence than if a surgical procedure had been done. In 76 percent of both the surgical-procedure-first and the medication-first cases, there was no recurrence.

It has recently been suggested that the combination of decongestants and antihistamines in the treatment of effusion causes existing fluid to thicken. To test this theory, we compared findings in cases in which drugs were prescribed before surgical treatment with findings in cases where medication was not prescribed. Of the group taking medicine, 72 percent had thick fluid, 23 percent had thin fluid and 5 percent had no fluid. In the nonmedicated cases, 74 percent had thick fluid, 14 percent had thin fluid and 12 percent had no fluid. If decongestants and antihistamines taken in combination caused thickening of fluid, patients receiving these drugs before surgical treatment would be expected to show proportionally more evidence of thick fluid than patients not receiving medication. Nearly identical results for the two groups do not support this contention.

In those cases where no fluid was found at operation, tubes were placed in the tympanic membranes when there was a history of recurrent bouts of acute otitis media and effusion.

Effectiveness of Specific Drugs

The most commonly recommended drug was Actifed, a combination of pseudoephedrine hydrochloride and tripolidine hydrochloride; it was the only drug whose use resulted in a greater than 50 percent success rate (62 percent) (Table 3). Pseudoephedrine (Sudafed) alone was successful in just less than half of the cases. Sudafed, which

TABLE 1.—*Factors Affecting Choice of Initial Treatment of 500 Children With Middle Ear Effusion*

Initial Treatment	*Duration of Problem (months)*		*Hearing Loss >25 dB (percent)*	*Previous Surgical Procedures (percent)*	*Speech/ Academic Delay*	
	Mean	*SD*			*Number*	*(percent)*
Medical	10.5	12.7	67	9	50/187	(27)
Surgical	17.1	9.7	70	27	36/104	(35)

TABLE 2.—*Comparison of Effectiveness of Different Treatment Strategies in 500 Children With Middle Ear Effusion*

Treatment Strategy	*Number*	*Resolution of Hearing Loss (months)*		*Recurrence Rate (percent)*	*Type of Fluid at Operation*		
		Mean	*SD*		*Thick (percent)*	*Thin (percent)*	*None (percent)*
Treated medically	153	4.8	2.1	24	..	..	..
Treated medically, then surgically	170	3.4	2.1	..	72	23	5
Initially treated surgically	177	1.6	2.1	24	74	14	12

contains only a decongestant, was the only drug that did less well when combined with an antibiotic. Dimetapp (brompheniramine maleate, phenylephrine hydrochloride and phenylpropanolamine hydrochloride) and Triaminic Syrup (phenylpropanolamine, pheniramine and pyrilamine) both did very poorly when administered alone, but improved in incidence of success from 20 percent to 40 percent when combined with an antibiotic. Finally, an interesting trend was the relative success of amoxicillin trihydrate compared with erythromycin. The number of cases in which a child was placed on a regimen of amoxicillin and an antihistamine-decongestant blend was unfortunately quite small. We will be evaluating the relative effectiveness of these two antibiotics in the future.

Discussion

Each physician will interpret results of the present study in light of his or her individual philosophy of optimum treatment. Certain implications, however, are clear. If a physician seeks primarily to minimize the delay in resolution of middle ear effusion and mild hearing loss, a strong case can be made for early surgical intervention. The average length of delay for cases in which medication was administered initially was three times as great (4.8 months versus 1.6 months) as for cases in which a surgical procedure was done immediately.

If minimizing delay is not the first priority, conservative management of effusion might indicate initially a regimen of antibiotics, decongestants and antihistamines. The incidence of recurrence of effusion was no greater in the children who were initially treated medically than in the children initially treated surgically. Thick fluid was also found in the same proportion in the former group as in the surgically treated cases. Thus, medication did not appear to result in thickening of fluid.

There are, of course, risks associated with either treatment strategy. Again, each physician will have to weigh the risks when initiating a specific treatment for effusion. The risk associated with the use of drugs is simply that they may not resolve effusion and delay may result in adverse effects on language acquisition. Medication was unsuccessful in 52 percent of these cases. The risks associated with myringotomy are surgical and are reviewed by Harell and Shea.[5]

Examination of the results also shows that for our physicians, the duration of hearing loss and past surgical history were the most influential factors in deciding between a surgical procedure first or medication first. The average duration of hearing loss was nearly twice as long for the initially surgically treated group as for the medically treated group. Degree of hearing loss was also not a factor. Fortunately, degree of hearing loss was not related to whether drugs were successful. Just as many children with hearing losses greater than 25 dB as with lesser loss had resolution of effusion from medical therapy.

Of the 500 children in the study, four were not

TABLE 3.—*Relative Success and Failure of Decongestants and Antihistamines With and Without Antibiotics for Treatment of Middle Ear Effusion (MEE)*

Drug	*Name and Manufacturer*	*Successful Resolution*		*Failed to Resolve MEE*		*Total Number Patients*
		Number	*(percent)*	*Number*	*(percent)*	
Pseudoephedrine HCl, tripolidine HCl	Actifed, Burroughs Wellcome	58	(62)	36	(38)	94
Plus erythromycin		6	(75)	2	(25)	8
Pseudoephedrine HCl	Sudafed, Burroughs Wellcome	37	(49)	39	(51)	76
Plus erythromycin		6	(30)	14	(70)	20
Brompheniramine mal., phenylephrine HCl, phenylpropanolamine HCL	Dimetapp, Robins	8	(27)	22	(73)	30
Plus erythromycin		16	(46)	19	(54)	35
Plus amoxicillin trihydrate		5	(71)	2	(29	7
Phenylpropanolamine HCl, pheniramine mal., pyrilamine mal.	Triaminic Syrup, Dorsey	6	(19)	25	(81)	31
Plus erythromycin		5	(56)	4	(44)	9
Erythromycin alone		6	(46)	7	(54)	13
	TOTALS	153		170		323

HCl = hydrochloride; mal. = maleate

effectively treated either medically or surgically and, accordingly, were considered candidates for mild gain, low maximum-power-output hearing aids. In each of these four patients, collar-button tubes had been placed in the tympanic membranes several times without success and were finally replaced by permanent mesh tubes. These children also had been taking decongestants, antihistamines and, occasionally, antibiotics. Two of the four children while on medical therapy were using autoinflation daily. Clearly tubes are not a panacea. To minimize significant effects of ongoing mild conductive hearing loss in children whose middle ear effusion is resistant to treatment, a mild-gain hearing aid should be recommended.

In 99 percent of the cases reviewed, medical or surgical treatment resolved middle ear effusion in an average of less than four months. This seems an insignificant period to adversely affect speech and language acquisition. However, it must be remembered that most of these children who were referred to the Otologic Medical Group had fairly long histories of middle ear problems. Thus, minimizing delay might well be of great importance.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Cochlear Implants for Deafness

QUESTION:

Are cochlear implants considered an experimental procedure?

OPINION:

The Advisory Panel on Otolaryngology reviewed its 1977 recommendation on cochlear implants for deafness. The panel now considers the procedure to be accepted medical practice when it is being done by physicians approved by the Food and Drug Administration. However, the panel believes the procedure should be monitored so that other, less qualified individuals do not attempt application of the procedure.

Refer to: Pezner RD, Lipsett JA: Peptic ulcer disease and other complications in patients receiving dexamethasone palliation for brain metastasis. West J Med 1982 Nov; 137: 375-378

Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis

RICHARD D. PEZNER, MD, *and* JAMES A. LIPSETT, MD, *Duarte, California*

A retrospective analysis was done of 106 patients who received radiation therapy for brain metastasis. Dexamethasone therapy was instituted in 97 patients. Peptic ulcer disease developed in 5 of 89 patients (5.6 percent) who received a dosage of at least 12 mg a day, but did not occur in patients who received a lower dose or in those who did not receive steroids. The interval between institution of dexamethasone therapy and the development of peptic ulcer disease ranged from three to nine weeks. Two patients had perforated ulcers, one of whom required surgical resection. Peptic ulcer disease contributed to the general deterioration and death of three of the five patients. Overall, in 14 of the 89 patients (15.7 percent) a complication of steroid therapy developed in the form of peptic ulcer disease, steroid myopathy or diabetes mellitus (or a combination of these).

CORTICOSTEROIDS HAVE BEEN SHOWN to be extremely effective in relieving the symptoms of cerebral edema due to primary or metastatic tumors in the brain.[1-3] Dexamethasone is one of the most commonly used agents. Side effects and complications of steroid therapy are recognized and one of the major potential complications associated with corticosteroid therapy is the development of peptic ulcer disease.[4,5] We review the use of dexamethasone in patients receiving radiation therapy for brain metastasis and the subsequent appearance of peptic ulcer disease and other complications.

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Submitted, revised, May 17, 1982.

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Patients and Methods

A retrospective analysis was done of patients at the City of Hope National Medical Center who received radiation therapy for brain metastasis between June 1977 and June 1981. Excluded from analysis were patients who received radiation therapy to the brain for hematologic malignancies, meningeal carcinomatosis, skull metastasis without intracranial disease or small cell undifferentiated bronchogenic carcinoma without intracranial disease.

There were 106 patients available for review,

TABLE 1.—*Patients With Brain Metastasis Distributed According to Primary Site*

Primary Tumor Site	*Number of Patients*
Lung	38
Breast	24
Skin (melanoma)	11
Gastrointestinal tract	10
Genitourinary tract	10
Head and neck	4
Other (thymus, cervix, pleura, bone)	4
Unknown primary	5
TOTAL	106

50 of whom were male and 56 female. The age of the patients ranged from 11 to 81 years with an average age of 54 years. Table 1 shows the distribution of patients by the primary site of the cancer.

Brain metastasis was diagnosed in all patients by radionuclide brain scan, computerized tomography or cerebral angiography (singly or in combination). Diagnosis of a malignant neoplasm was confirmed by pathology studies in all patients. Five patients underwent craniotomy as the initial treatment. All patients received radiation therapy to the entire brain, a broad range of dose schedules being used. Anticonvulsant medication was administered to 17 patients. Misonidazole (an experimental orally given drug related to the antiprotozoal agent metronidazole) which is currently being evaluated as a potential agent to increase the radiosensitivity of tumors was concurrently given to six patients who were receiving treatment according to protocols of the Radiation Therapy Oncology Group.

Dexamethasone therapy was instituted in 97 patients at the time of diagnosis of brain metastasis and was the only corticosteroid used. The standard dose was 4 mg given orally every six hours. The total dosage was at least 12 mg per day in 89 patients and 8 mg or less a day in eight patients. Nine patients with minimal or no neurologic symptoms did not receive steroid therapy. In only one patient was therapy started with a dosage of greater than 24 mg a day. The daily dosage was increased to greater than 24 mg in several patients whose neurologic symptoms worsened while they were receiving radiation therapy. Dexamethasone administration was continued during the course of radiation therapy until it was judged that a sufficient radiation dose had been delivered for tumor shrinkage to occur. This was a minimum of two weeks in most patients. The dexamethasone dosage was then gradually tapered during a period of one to three weeks until administration of the drug was discontinued. Many patients, however, required steroid therapy on a long-term basis to suppress persistent neurologic symptoms.

All patients were observed for a minimum of three months after the institution of dexamethasone therapy. Statistical significance was tested by the x^2 method.[6]

Results

In 5 of the 89 patients (5.6 percent) receiving at least 12 mg of dexamethasone a day peptic ulcer disease developed (Table 2). This complication did not occur in patients who received a lower dosage of dexamethasone or in those who received no steroid therapy. The five patients in whom peptic ulcer disease developed ranged in age from 42 to 60 years; three were men and two were women. Four of the five had known distant metastasis at sites other than the brain. All five had received systemic chemotherapy, three concurrently at the time of diagnosis of brain metastasis and two at some time in the past. Presenting neurologic symptoms in three patients were either mild or controllable by nonsteroid medication given orally. These included headaches, nausea, vomiting, seizures and transient visual auras. One patient had mild right hemiparesis and aphasia. Another patient had symptoms of vertigo, incoordination and confusion. None of the five patients were stuporous, somnolent or comatose. Four of the five had multiple metastatic lesions in the brain. None, however, had massive lesions producing either midline shift or obstructive hydrocephalus. Metastatic lesions were located solely in the cerebral hemispheres in four patients and in both the cerebrum and cerebellum in one. In one patient, the metastatic lesions were found to be due to direct invasion from skull lesions, whereas in the other four patients they were considered to be hematogenously transmitted. None of the five patients underwent craniotomy at any time during their clinical course.

The interval between the institution of dexamethasone therapy and the development of peptic ulcer ranged from three to nine weeks. In only one patient did an ulcer appear in less than six weeks. Two of the five patients were prophylactically placed on antacids while receiving steroids.

TABLE 2.—*Patients in Whom Peptic Ulcer Disease (PUD) Developed After Receiving Dexamethasone*

Case	Age/Sex	Primary Tumor: Site	Primary Tumor: Histologic Diagnosis	Interval From Primary to Brain Metastasis (mos)	Dexamethasone: Total Daily Dose (mg)	Dexamethasone: Duration to PUD (wks)	Symptoms of PUD	Peptic Ulcer: Site	Peptic Ulcer: Perforation	Survival Status After PUD Diagnosis
1	42/♀	Lung	Small cell	0	16	3	Pain × 8 days	Gastric	No	Died 8 mos
2	52/♂	Prostate	Adenocarcinoma	40	16	6	Sudden onset of pain	Duodenal	Yes	Died 2 mos*
3	56/♂	Lung	Adenocarcinoma	56	16	8	Sudden onset of pain	Gastric	Yes	Died 2 mos*
4	51/♂	Skin	Melanoma	80	24	7	Lower gastrointestinal tract bleeding	Duodenal	No	Died 2 wks*
5	60/♀	Breast	Adenocarcinoma	22	12	9	Pain × 7 days	Gastric	No	Died 8 mos

*Peptic ulcer disease contributed to general deterioration and demise of patient.

Tapering of dexamethasone dosage had been started in two patients before the peptic ulcer disease developed.

Possible associated factors were noted in four patients, including three who were using aspirin, aspirin-containing medication or indomethacin for pain relief, two patients who had thrombocytopenia, and one patient who had a history of prolonged ethanol abuse. One patient reported a history of peptic ulcer disease, though this could not be confirmed.

Symptoms were sudden onset of severe epigastric pain in two patients, epigastric pain of several days' duration in two patients and bleeding per rectum in one patient. Three patients had gastric ulcers and two had duodenal ulcers. The diagnosis was made by upper gastrointestinal x-ray series in four cases and by exploratory laparotomy in one. Both patients with abrupt onset of pain had perforated ulcers, one a gastric ulcer and the other a duodenal ulcer. Four were treated by nonsurgical means, including administration of antacids, cimetidine, blood transfusions or antibiotics (or a combination of these). The patient who had an exploratory laparotomy was found to have a perforated gastric ulcer and underwent a Bilroth-II procedure with resection of 70 percent of the stomach. Ulcers resolved in two patients, but contributed to the general deterioration and demise of the other three patients.

Further analysis of the 89 patients who received at least 12 mg of dexamethasone a day showed that neither misonidazole nor anticonvulsant medication produced a statistically significant difference in the frequency of peptic ulcer disease. This complication occurred in one of six patients (16.7 percent) who received misonidazole and in 4 of 83 patients (4.8 percent) who did not. It developed in 1 of 13 patients (7.7 percent) who received anticonvulsants and in 4 of 76 (5.3 percent) who did not.

Other complications of long-term steroid therapy were found. Steroid myopathy was diagnosed in four patients. The development or exacerbation of diabetes mellitus (that is, symptomatic hyperglycemia requiring medical treatment) occurred in six patients. Three of the six had a history of adult-onset diabetes mellitus. One patient suffered both myopathic and diabetic complications. All patients with these two complications had received at least 12 mg of dexamethasone a day. Overall, in 14 of the 89 patients (15.7 percent) taking at least 12 mg of dexamethasone a day, a complication of steroid therapy developed in the form of peptic ulcer disease, steroid myopathy or diabetes mellitus.

Discussion

Peptic ulcer disease and gastrointestinal bleeding are recognized complications of corticosteroid therapy.[2,4,5] Their development has been evaluated in detail in neurosurgical patients. Peptic ulcer disease may appear as stress ulcers following craniotomy in patients with intracranial disease.[7] It occurs more frequently, though, when neurosurgical patients are also receiving steroids. Gastrointestinal bleeding has been reported in 0.3 percent to 4.0 percent of patients not receiving steroids and in 1.5 percent to 16.5 percent of patients receiving steroids.[7-9] The duration of steroid administration in neurosurgical patients is usually seven to ten days. Gastrointestinal bleeding occurred mainly in comatose, respirator-dependent patients who required steroids for more than ten days.[7,9] Gastrointestinal bleeding may have been the result of the stress of the respirator,

but may also have been the result of a prolonged course of steroid therapy.

Peptic ulcer disease has also been reported in patients with neurologic diseases who did not undergo craniotomy. Ottonello and Primavera[10] showed in an autopsy study that in patients with acute cerebrovascular accident, there was a greater incidence of peptic ulcers in those who received steroids than in those who did not. Graham and Caird[11] noted that peptic ulcer disease developed in 1 of 20 patients who received steroids to palliate the symptoms of a brain tumor. Greenberg and co-workers[12] noted a 1.2 percent incidence of peptic ulcer disease in patients receiving steroids while undergoing radiation therapy for spinal cord compression due to epidural metastatic cancer. They used dexamethasone in a regimen that started with a dosage of 96 mg a day, which was then rapidly tapered and its use discontinued in two weeks.

The present study shows an incidence of peptic ulcer disease of 5.6 percent in patients receiving a dosage of dexamethasone of at least 12 mg a day. This complication appeared in patients who were ambulatory with only mild to moderate neurologic symptoms and who had not undergone craniotomy. It appeared only in patients who required that a dosage of at least 12 mg of dexamethasone a day be maintained for several weeks. This complication is serious because it may appear suddenly in the form of a perforated viscus and may lead to the deterioration and death of a patient.

The concurrent use of anticonvulsant medication or the radiosensitizer agent misonidazole did not appear to alter the incidence of peptic ulcer disease. Concurrent use of known ulcerogenic agents such as aspirin or indomethacin may increase the risk of a peptic ulcer developing.

In summary, dexamethasone and other corticosteroids are highly effective for rapidly palliating the symptoms of brain metastasis. Yet, because of the risk of the potentially serious complications of peptic ulcer disease, diabetes mellitus and steroid myopathy, corticosteroid dosage should be tapered and administration eventually discontinued as soon as radiation therapy has provided symptomatic relief. For patients with minimal or no neurologic symptoms, the use of steroids should be considered carefully in view of the risk of complications.

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Refer to: Kerndt PR, Naughton JL, Driscoll CE, et al: Fasting. The history, pathophysiology and complications (Medical Progress). West J Med 1982 Nov, 137 379-399

Fasting: The History, Pathophysiology and Complications

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An appreciation of the physiology of fasting is essential to the understanding of therapeutic dietary interventions and the effect of food deprivation in various diseases. The practice of prolonged fasting for political or religious purposes is increasing, and a physician is likely to encounter such circumstances. Early in fasting weight loss is rapid, averaging 0.9 kg per day during the first week and slowing to 0.3 kg per day by the third week; early rapid weight loss is primarily due to negative sodium balance. Metabolically, early fasting is characterized by a high rate of gluconeogenesis with amino acids as the primary substrates. As fasting continues, progressive ketosis develops due to the mobilization and oxidation of fatty acids. As ketone levels rise they replace glucose as the primary energy source in the central nervous system, thereby decreasing the need for gluconeogenesis and sparing protein catabolism. Several hormonal changes occur during fasting, including a fall in insulin and T_3 levels and a rise in glucagon and reverse T_3 levels. Most studies of fasting have used obese persons and results may not always apply to lean persons. Medical complications seen in fasting include gout and urate nephrolithiasis, postural hypotension and cardiac arrhythmias.

WE REVIEW IN THIS PAPER the current understanding of the pathophysiology of fasting and starvation. Although fasting implies an intentional abstention from food, the physiologic adaptive mechanisms (not necessarily psychologic) that come into play during this type of food deprivation are similar to starvation. These terms will be used synonymously, therefore, except when important differences are known to exist.

An appreciation of the physiology of fasting is essential for understanding many kinds of therapeutic dietary manipulations. Critical evaluation of protein-sparing diets, ketogenic diets or other hypocaloric mixed-diet regimens requires a knowledge of the response to acaloric fasting. Because many illnesses result in food deprivation, physicians should understand the usual physical and metabolic consequences of starvation; an illustra-

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

tive case that was monitored according to a study protocol is presented. The effects of fasting are reviewed in association with the individual effects observed in the case.

A study protocol was designed to monitor a fasting person and was submitted to and approved by the Human Experimentation Committee of the University of Iowa College of Medicine, Iowa City, Iowa.

A Brief History of Fasting

Since early times, fasting has been advocated for spiritual development and promotion of health. Fasting as a religious practice developed independently among different people and religions worldwide.[1] In ancient Greece the belief that taking food risked entry of demonic forces contributed to the popularity of fasting. Fasting was required in preparation for many rituals that sought contact with supernatural forces.[2] Great importance was placed on fasting as a means of arousing ecstatic forces, dreams or visions. Pythagoras, Abaris and Epimenides in ancient Greece extolled the virtues of fasting, and in biblical times Moses, Elias and John the Baptist recognized its religious value.[1] During the holy month of Ramadan, Moslems abstain from all food and drink between dawn and dusk.[3]

In the Old Testament fasting was regarded as a powerful prayer that could prepare a prophet for divine revelations (Daniel 10:2-14). Although Christ fasted for 40 days in the desert (Luke 4: 1-2; Matthew 4:2-3), he left no definite law on the subject except to insist that it be done humbly and privately (Matthew 6:16-18). With time, customary observances of fasting developed in local Christian churches partly in an effort to replace early pagan and Jewish fasting customs. Fasting in the monastic tradition flourished in the fourth and fifth centuries, the dominant motive being asceticism guided by a spirit of penance and self-humiliation as a monk sought communion with his God.[1] The motive for the case reported in this paper was consistent with the monastic tradition and was a prayerful penitential response to modern-day social injustice.

Historically, fasting for health has been advocated by many.[1,5] In the mid-1800's, E. H. Dewey, MD, in his book *The True Science of Living,* wrote, "every disease that afflicts mankind [develops from] more or less habitual eating in excess of the supply of gastric juices." His "miraculously cured" patient and later publisher, Charles Haskell, did much to promote the fasting cure.[4] Upton Sinclair, better known for other literary works, wrote extensively on the health benefits of fasting.[5]

Notable nonobese persons who engaged in prolonged fasting and whose experiences were recorded in the early medical literature include Tanner who reportedly fasted for 40 days in 1880.[6,7] Alexander Jacques, a Frenchman, fasted for 30 days in 1887 and for 40 and again 30 days in 1888.[7] Signor Succi, an Italian professional faster, claimed to have completed at least 32 fasts of 20 days or more[8]; his longest recorded fasts were 40 and 45 days in 1890.[9] In 1905 a physician, F. Penny, MD, prompted by the claims of Dewey, fasted for 30 days and recorded simple observations on himself.[10] Observations during fasts in nonobese persons are less extensively recorded in the modern medical literature. Benedict's classic study in 1912 of Mr. L, who fasted for 31 days, included detailed physical and metabolic measurements.[9] In 1946 Bernard came under medical observations on the 40th day of a purported 45-day fast.[11] About the same time, Gamble's classic life-raft studies, wherein volunteers were subjected to food and water deprivation under conditions simulating being lost at sea, did much to elucidate the essential water requirements and protein-sparing effect of carbohydrate.[12] In the early 1950's Ancel Keys and co-workers[13] at the University of Minnesota compiled extensive data on 32 volunteers who underwent eight months of semistarvation.

Fasting as a therapy for obesity has long been advocated. Folin and Denis in 1915[14] recommended repeated short periods of starvation as a safe and effective method of weight reduction. In modern times Bloom,[15] Duncan and associates[16] and Drenick and colleagues[17] advocated prolonged fasts for weight reduction in morbid obesity. Drenick and colleagues[17] placed obese persons on fasting regimens of up to 117 days, whereas Thomson and co-workers[18] monitored fasts of 139, 236 and 249 days. The longest recorded fast was that of a 27-year-old obese man who fasted 382 days and lost 125 kg (276 lb).[19] Since the late 1950's many of the data on the metabolism of

fasting come from studies carried out on obese persons willing to fast for weight reduction.

Fasting for the treatment of convulsive disorders was used in France by Guelpa and Marie in 1910 (as cited by Keith[20]) and later investigated here by Geyelin in 1921.[21] Changes in the acid-base balance were originally thought to be responsible for the anticonvulsant effect until Wilder in 1921 (also cited by Keith[20]) suggested a role for starvation-induced ketone bodies. Since that time, ketogenic diets have been used successfully in the management of seizure disorders refractory to conventional drug regimens.[22]

Fasting has often been used as a means of political protest. Gandhi fasted for political reasons on at least 14 occasions, 3 times for as long as 21 days.[23] One of the longest recorded political fasts in a nonobese person was by Terence MacSwincy, a former mayor of Cork, who fasted for 74 days to his death after his arrest during English-Irish unrest in 1920.[24] Joseph Murphy, less well known but also a member of the Irish Volunteers, died on the same day as MacSwiney after 76 days of a hunger strike.[24] The hunger strike as a means of political persuasion is being used still in Ireland: To date ten members of the Irish Republican Army have fasted from 45 to 61 days to their death in the now-infamous H block of the Maze prison in Belfast, Northern Ireland.[25]

Study Protocol

A complete physical examination, including an electrocardiogram and a roentgenogram of the chest, was carried out before the fast. Laboratory determinations that were also done included serum potassium, chloride, calcium, phosphorus, uric acid, creatinine, total protein, albumin, globulin, triglycerides, total lipids, total bilirubin, direct bilirubin, aspartate aminotransferase (glutamic-oxaloacetic transaminase), alanine aminotransferase (glutamic-pyruvic transaminase), alkaline phosphatase, lactic dehydrogenase, thyroxine, iron, blood urea nitrogen, glucose and a complete blood count, including a differential cell count, using standard methods at METPATH, Teterboro, New Jersey.* Insulin, glucagon, growth hormone and plasma amino acid levels were measured using methods reported elsewhere.[26-29] Follicle-stimulating hormone and luteinizing hormone levels were measured using standard radioimmunoassay techniques. Zinc concentration was measured using a Perkin-Elmer atomic spectrometer. A urine specimen was collected for measurement of total volume and pH, qualitative determination of ketones, protein, blood, bilirubin and glucose, and quantitative determinations using standard methods for sodium, potassium, chloride, calcium, phosphorus, magnesium, urea, ammonia, creatinine, uric acid and total nitrogen.

Fluid intake (water only) was initially two liters a day for the first three weeks, then decreased to and maintained at a liter per day during the final week of the fast. A total intake of 60 calories from daily communion was recorded during the fast. The subject was ambulatory throughout the fasting period and was weighed daily on arising and after voiding. Pulse rate and blood pressure were determined twice a day. Electrocardiograms were obtained weekly. Complete physical examinations were done weekly for the first three weeks, followed by daily physician visits (provided by James Pearson, MD, Dubuque, Iowa) in the last ten days of the fast. Medical consultation was available by telephone at any time or by a physician visit within 20 minutes. All laboratory tests were repeated weekly except a dipstick urine analysis, which was done daily.

Case Report and Review of the Literature

A 41-year-old nonobese man, a member of a cloistered religious community, chose to undergo a 40-day acaloric fast. He requested that his fast be supervised medically to minimize any risk to his health. Monitoring was to be carried out within the confines of the monastic enclosure without undue distraction from the intent of the fast while maintaining strict anonymity for himself and his religious community. After all risks including the possibility of sudden death were discussed, a form releasing us from legal liability was signed. Furthermore, it was agreed that the fast could be terminated at any time either by him or upon medical recommendation. The past medical history was significant for occasional benign ventricular premature contractions and iron deficiency anemia. His usual diet had been ovolactovegetarian (that is, vegetables, eggs and milk products) for the preceding 24 years.

Control Data

On physical examination before commencement of the fast the man weighed 68.6 kg, was 172 cm tall and appeared in no acute distress. His skin

*Drs. L. J. Filer, L. D. Stegink, R. Thompson and D. E. Van Orden at the University of Iowa made available the use of their laboratory facilities and personnel for preparing many of the determinations for this study.

TABLE 1.—*Mean Blood Pressure and Pulse Changes in the Upright and Supine Positions at Weekly Intervals in the Fasting and Realimentation Periods*

Day of Study	Supine: Mean Blood Pressure (torr)	Supine: Mean Pulse Rate (beats/min)	Upright: Mean Blood Pressure (torr)	Upright: Mean Pulse Rate (beats/min)
Fasting Period				
1-7	110/66 (128-96)/(82-58)*	55 (60-48)	107/75 (124-92)/(92-64)	73 (90-64)
8-14	108/64 (112-98)/(76-58)	54 (60-50)	90/65 (96-86)/(72-58)	88 (106-70)
15-21	104/62 (110-98)/(66-60)	55 (60-50)	80/54 (92-72)/(58-46)	82 (96-68)
22-28	100/61 (114-92)/(72-52)	57 (60-54)	72/54 (84-64)/(62-50)	86 (90-78)
29-36†	92/53 (98-88)/(60-46)	56 (58-54)	70/51 (76-64)/(58-46)	83 (92-78)
Postfast Period				
1-7	100/59 (112-88)/(80-60)	60 (66-56)	70/53 (78-62)/(62-42)	96 (112-80)

*Range included in parentheses.
†Mean calculated on the basis of an 8-day period.

was clear and the head, eyes, ears, nose and throat showed no abnormalities. Examination of the chest showed a mild pectus excavatum and the lungs were clear to auscultation and percussion. On cardiac examination there were normally split first and second heart sounds with a grade 2/6 systolic ejection murmur present along the left sternal border without radiation or change with the Valsalva maneuver or position. The abdomen was soft, nontender and without evidence of hepatosplenomegaly. Prostatic enlargement was noted on examination of the rectum. Guaiac test of a stool specimen was negative for occult blood. No clubbing, cyanosis or edema was present in the extremities. Peripheral pulses were normal. There was no lymphadenopathy. On neurologic examination there were no abnormalities found.

An electrocardiogram showed sinus bradycardia with a rate of 45 to 50 beats per minute and an incomplete right bundle branch block. A treadmill exercise stress test done 16 months earlier showed no abnormalities at 100 percent of maximal predicted heart rate. An x-ray film of the chest showed only the small pectus excavatum deformity.

Physical Adaptations to Fasting

The subject fasted for 36 days until profound weakness and symptoms of postural hypotension interfered with his daily activities in the monastery.

Weight Loss

He lost 15.7 kg or 22.9 percent of his initial body weight after 36 days of acaloric fasting. Weight loss continued through the first two days of realimentation, resulting in a total weight loss of 16.6 kg or 24.2 percent of initial body weight. The rate of weight loss was initially 0.9 kg per day for the first five days, then it gradually decreased over the next two weeks and became stable at 0.3 kg per day after the third week.

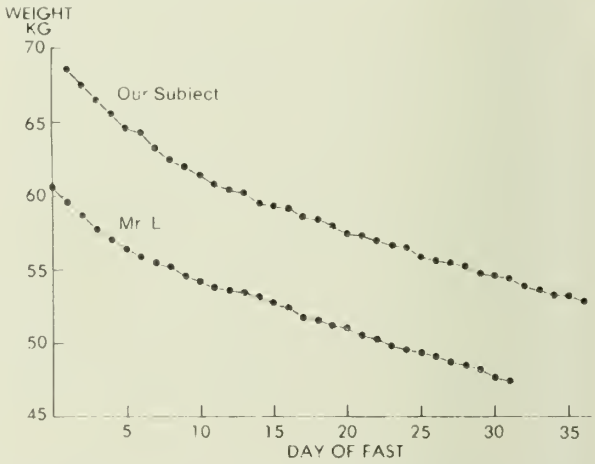

Figure 1.—Rate of weight loss during total fasting in our subject and Mr. L, studied by Benedict in 1912.[9]

The total weight loss and the rate of loss compare favorably with those reported elsewhere: In the initial fasting period (one to five days), weight loss occurs at the rate of 1 to 2 kg per day followed by a gradual decline through the third week, thereafter averaging 0.3 kg per day.[30] In Benedict's study,[9] Mr. L lost 13.25 kg or 21.9 percent of initial body weight after 31 days of fasting. This compares with a 14.2-kg loss or 20.7 percent of initial body weight after the same time in our subject (Figure 1).

Pulse Rate

Our subject's pulse rate did not decrease significantly during fasting (Table 1). This may reflect the presence of bradycardia in this well-conditioned man before onset of fasting. Slowing of pulse rate during prolonged periods of de-

ereased calorie intake is otherwise well documented.[9,13,31,32] Benedict[9] reported that the pulse rate reached a minimum during the second to third week of total fasting and then increased in the fourth week. In another study[13] of 32 volunteers on semistarvation diets for 32 weeks who had an average weight loss of 16 percent, the pulse rates steadily deelined, reaehing a mean of 35.3 beats per minute at 13 weeks; however, after an additional ten weeks of ealoric restriction and another 10 pereent reduetion in body weight, the pulse rates rose slightly but significantly to a mean of 37.3 beats per minute. In the studies by Jewish physicians during the siege of the Warsaw ghetto in World War II, bradycardia was seen in adults and ehildren in all stages of starvation.[33]

Blood Pressure

In our study the mean blood pressure ealeulated for weekly intervals fell from 110/66 mm of mereury during the first week to 92/53 mm of mereury during the last eight days of the fasting period (Table 1). Blood pressure inereased signifieantly toward prefast values in the realimentation period. Pronounced orthostatic hypotension oecurred by the seeond week and persisted throughout the fasting period. The subject became symptomatic after several days and was nearly ineapaeitated by the postural hypotension after 33 days, requiring 20 to 30 minutes to go from the supine to the upright position on rising in the morning. Subjeetively, the postural symptoms improved as the day progressed. There were no syncopal episodes during the fasting or realimentation periods.

A fall in blood pressure is a eonsistent observation during fasting and semistarvation states.[9,13,33,34] The development of symptomatic orthostatic hypotension during fasting is not predictable but seems to depend on the individual person, the duration and the type of fast. Drenick and colleagues[17] noted incapacitating postural hypotension in 3 of 11 obese persons after 25, 60 and 62 days of fasting. More reeently, seven obese patients placed on a regimen of 400 kcal of protein per day and later 400 kcal of a mixed diet (50 pereent protein, 50 pereent earbohydrate) per day were followed for periods of 3 to 5½ weeks.[35] While on the protein diet, the systolie blood pressure fell 28±3 mm of mercury versus 18±3 mm of mercury on the mixed diet. Symptoms of orthostatic hypotension developed in all patients while on the protein diet and in only one while on the mixed diet. Along with raised serum ketone levels and inereased salt excretion, plasma levels of norepinephrine were reduced in the basal state and after two minutes of standing in persons receiving the pure protein diet but not with the mixed diet regimen. The mechanism of the different effects of pure protein versus mixed diets on the sympathetic nervous system is not yet fully understood.

In another study using animals, an association between fasting and overfeeding with sucrose and rates of norepinephrine turnover was found.[36] A significant reduction in norepinephrine turnover was seen in food-deprived rats versus an increased turnover in rats overfed with suerose. Should a similar mechanism exist in man, an essential role for dietary carbohydrate in the maintenance of sympathetie nervous system function could be postulated.

Electrocardiograms

On our subjeet's electrocardiograms, shifts to the right of the QRS (30 degrees to 60 degrees) and to a lesser extent T-wave axis (50 degrees to 60 degrees) occurred. A decrease in amplitude from 6 to 3 mm was seen in the QRS complex only in lead I.

Changes in the electrocardiogram during fasting and semistarvation are well known.[13,31,34,37,38] Changes most frequently reported include sinus bradycardia, decreased QRS complex and T-wave amplitude, and shifts to the right of the QRS and T-wave axes. In the Minnesota semistarvation study,[13] a deerease in the amplitude of all defleetions (P wave, QRS complex and T wave) oecurred with a shift to the right of the QRS and T-wave axes; though the QT interval and duration of mechanieal systole increased, the PR and QRS intervals and the duration of the P wave did not change. In case reports of World War II prisoners suffering from severe malnutrition, reversible electrocardiographic abnormalities including pronounced prolongation of the QT interval, to a lesser extent lengthening of the PR and QRS intervals, depression of the ST segment and changes in the T wave were noted.[37] Similarly, prolongation of the QT interval and abnormal ST segment and T wave are consistent findings in patients with anorexia nervosa.[39]

The mechanism underlying these electrocardiographie changes is unknown. Atrophy of cardiac muscle has been observed in starvation.[37,38] and

many of these electrocardiographic changes may reflect decreased cardiac mass.

Natriuresis

The early high rate of weight loss in our subject cannot be explained on the basis of energy expenditure alone. If the initial 0.9 kg per day weight loss observed were to reflect loss of body fat, carbohydrate and protein, it would require an energy expenditure of 3,150 calories per day. This is far in excess of the basal energy expenditure[40] of 1,673 calories per day predicted for this man in the early fasting period. It is now well established that early accelerated weight loss during fasting is the result of salt and water diuresis.[41-43]

Because no attempt was made to equilibrate salt intake in the prefast period in our study, urinary sodium levels (as well as other electrolyte and mineral determinations) on day 1 reflect the previous unmeasured dietary intake. However, cumulative sodium loss was estimated at 325 mEq over the first seven days and the peak net urinary sodium loss was 68 mEq in one day and occurred on day 3. The sodium loss corresponded to an 0.9 kg per day weight loss and 0.9 liter negative fluid balance (insensible losses not included). Urinary chloride loss followed a similar pattern but was quantitatively less than sodium loss. Cumulative urinary sodium losses in the first week of fasting in our subject were comparable to those observed by others (200 to 350 mEq), but the peak sodium loss of 73 mEq on day 3 was somewhat less than the 100 to 150 mEq peak losses reported elsewhere to occur on fasting days 3 or 4.[30]

Numerous explanations have been offered for the early natriuresis during fasting including changes in renal tubule sodium-transport systems, glomerular filtration rate, aldosterone secretion, ketoacidosis or an osmotically induced diuresis.[30] All fail to explain this phenomenon entirely. It now appears that this natriuresis is, in large part, the result of obligatory sodium loss due to the generation and high early excretion of ketone bodies.[42,43] As liver glycogen stores are depleted and body energy requirements are met by mobilization of fat stores, serum and urinary levels of metabolically generated anions in the form of ketones increase. Excretion of these anions requires an accompanying cation that initially is sodium. Ammonium production increases under the stimulus of metabolic acidosis (ketoacidosis) and ammonium replaces sodium as the major

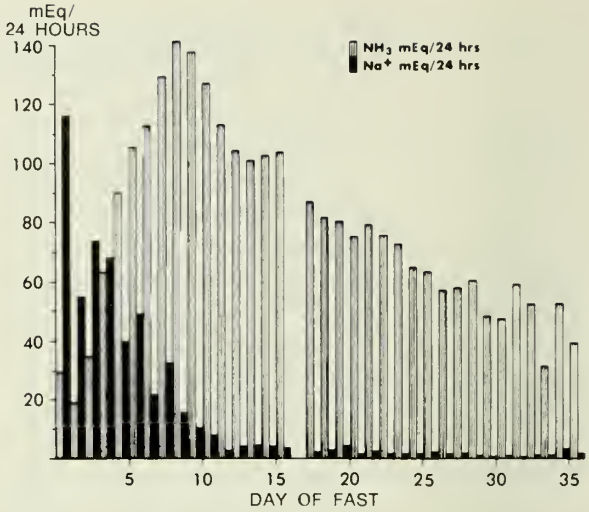

Figure 2.—Urinary sodium (Na^+) and ammonia (NH_3) losses during the fasting period.

urinary cation. During the period when urinary excretion of ammonium is lagging behind ketone excretion, peak rates of sodium excretion are observed (and maximum weight loss occurs).[42-44] This pattern was seen in our subject: urinary ammonia excretion increased through day 9 as sodium excretion gradually declined (Figure 2).

Hormonal mechanisms have also been implicated in the natriuresis of early fasting. Glucagon levels rise during this period; experimentally, infusions of physiologic doses of glucagon in nonfasting subjects induce a similar natriuresis[45] while administration of insulin can cause renal sodium retention.[46] Therefore, the rising glucagon and the falling insulin levels during the early phase of fasting may both contribute to sodium excretion.

Carbohydrate refeeding after fasting (though the diet may still be hypocaloric) produces an abrupt weight gain with an immediate reversal of urinary salt and water loss.[12,47-49] At times the sodium retention is profound, resulting in frank edema formation. Isocaloric refeeding with fat does not result in sodium retention whereas refeeding with protein produces a delayed but significant antinatriuresis.[48] The mechanism of sodium retention with carbohydrate realimentation is not well understood. Rising insulin and falling glucagon levels may be involved but are unlikely to account for frank edema formation. The aldosterone level is not consistently raised and usually falls with realimentation.[50] A reversal of this pattern of urinary excretion of solutes, namely persistent secretion of ammonium after suppression

of ketonuria by carbohydrate realimentation, could also contribute to sodium retention.

Metabolic Adaptation of Fasting

Fuel Stores

The composition of total body fuel stores in humans is well understood (Table 2). In fasting states liver glycogen is depleted in the first 18 to 24 hours.[30] Protein, which has essential enzymatic, structural and mechanical functions, constitutes 15 percent of total body energy stores.[51] Because of these essential functions, the breakdown of a third to a half of the body protein stores is believed incompatible with life.[52] Muscle, another site of glycogen stores, lacks glucose-6-phosphatase and therefore cannot release glucose directly into the bloodstream.[53] Fat in the form of triglycerides in adipose tissue provides the largest and most efficient storage of body energy and constitutes 85 percent of all potentially available calories.[51] In a 70-kg person basal caloric requirements could be met solely from fat stores for two to three months in the absence of any caloric intake.[51,53,54]

Glucose Homeostasis

In our subject blood glucose levels fell early during fasting and remained low throughout the fasting period. Insulin levels became appropriately reduced as glucagon increased significantly (Table 3).

The transition from the fed state through brief fasting and into prolonged starvation is mediated by a series of complex metabolic, hormonal and glucoregulatory mechanisms. The interrelationship between body fuel stores and the time sequence for their mobilization via glycogenolysis, gluconeogenesis, lipolysis and ketogenesis is diagramed in Figure 3. Felig[30] conveniently divided the transition from a fed to a fasted state into three stages: (1) the postabsorptive phase, 6 to 24 hours after beginning fasting, during which cerebral glucose requirements are maintained primarily via glycogenolysis, (2) the gluconeogenic phase, from two to ten days of fasting, during which glucose requirements are met using gluconeogenic amino acids, lactate, pyruvate and glycerol, and (3) the protein conservation phase beyond ten days of fasting, characterized by decreasing protein catabolism as fat stores are mobilized and tissue use of free fatty acids and ketones increases.

In the postabsorptive state, total glucose use is

TABLE 2.—*Body Fuel Stores of Healthy Humans**

Body Fuel Source	*Kg*	*Calories*	*Percent of Total Fuel*
Fat (adipose)	15.0	141,000	85.00
Protein (mainly muscle)	6.0	24,000	14.50
Glycogen (muscle)	0.150	600	0.35
Glycogen (liver)	0.075	300	0.15

*Modified from Cahill et al.[51]

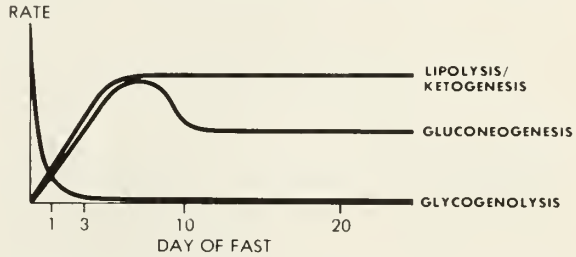

Figure 3.—A schematic of the changes in rates of glycogenolysis, gluconeogenesis, lipolysis and ketogenesis that are required to maintain caloric homeostasis during the transition from brief to prolonged fasting.

TABLE 3.—*Serum Glucose, Insulin, Glucagon, Growth Hormone, Total Lipids and Triglyceride Levels in Our Subject Before, During and After Fasting*

Day of Study	*Glucose (mg/dl)*	*Insulin (μIU/ml)*	*Glucagon (pg/ml)*	*Growth Hormone (ng/ml)*	*Total Lipids (mg/dl)*	*Triglycerides (mg/dl)*
Prefast Period						
	96	13.5	138.7	0.73	530	72
Fasting Period						
5	63	2.91	222.1	2.92	430	118
12	74	5.31	161.8	4.10	440	122
19	71	2.64	248.5	7.95	410	136
26	77	1.50	327.8	9.86	400	101
33	76	1.34	727.8	3.12	470	111
36	56	2.55	198.2	4.51	400	124
Postfast Period						
7	135	16.0	218.9	0.82	500	314
12	90	...	...	...	470	125

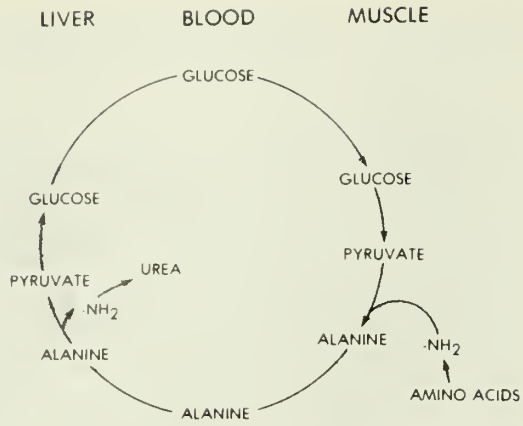

Figure 4.—The glucose-alanine cycle. Glucose released by the liver is taken up by muscle where it is converted to pyruvate and transaminated to form alanine. The alanine thus synthesized is released by muscle and taken up by the liver where its carbon skeleton is reconverted to glucose, thus completing the cycle (from Felig[55]).

150 to 250 grams per day.[54] The brain consumes the largest fraction, about 125 to 150 grams, while resting muscle cells and obligate anaerobic cells in bone marrow, blood, peripheral nerve and renal medulla consume the remainder.[55] Hepatic glycogenolysis provides about 75 percent of the glucose requirements early in fasting from its glycogen reserve of 70 grams.[55] The remainder comes from gluconeogenic precursors: amino acids (10 percent to 15 percent), lactate and pyruvate (10 percent to 15 percent) and glycerol (1 percent to 2 percent).[55] Muscle glycogen is metabolized to lactate that is released into the circulation and is resynthesized into glucose by the liver and kidney. Although this process (the Cori cycle) results in no net production of glucose, an advantage exists in that glucose synthesis from protein catabolism is reduced and the energy for resynthesis is derived from the oxidation of free fatty acids, a plentiful and readily available energy source.[56] Glycerol, a by-product of the hydrolysis of triglycerides and release of free fatty acids, provides a small but significant nonprotein-derived gluconeogenic precursor in prolonged fasting.[55] Thus, although humans cannot synthesize glucose directly from fat, the energy derived from oxidation of free fatty acids facilitates glucose synthesis from lactate and glycerol.

As mentioned earlier, gluconeogenesis from protein-derived amino acids provides 10 percent to 15 percent of the substrate in the early fasting period. Although all amino acids except leucine are potentially gluconeogenic, a specific pattern of precursor availability occurs. Alanine, which constitutes no more than 7 percent to 10 percent of all amino acid residues in skeletal muscle, accounts for 30 percent to 40 percent of amino acids released from muscle after an overnight fast.[55] It is now well established that this increased output represents de novo alanine synthesis in muscle by transamination of pyruvate.[55]

Felig and associates[57] noted that the concentrations of branched chain amino acids (valine, leucine, isoleucine) are increased early in fasting, reaching a peak at approximately the fifth day. These amino acid and serum alanine levels rose early during the fasting period in our subject. The branched chain amino acids appear to be preferentially catabolized in muscle and provide the nitrogen source for the transamination of pyruvate to alanine.[58] Subsequently, the alanine released by muscle is taken up by the liver and kidney where it is resynthesized into glucose.[57] The amino groups are converted to urea, which is excreted in the urine. This glucose-alanine cycle, which is comparable to the Cori cycle discussed earlier, represents a major glucohomeostatic mechanism in the early fasting period (Figure 4). This cycle provides a source of alanine that the liver uses, more efficiently than it uses any other amino acid, to make glucose.[57] It also establishes several control points for feedback inhibition of gluconeogenesis—that is, insulin reduces gluconeogenesis by inhibiting hepatic alanine uptake,[57] and ketosis inhibits gluconeogenesis[59] by decreasing the degradation of branched chain amino acids that in turn removes the source of nitrogen for alanine synthesis.

As fasting progresses, plasma glucose levels fall significantly whereas the level of glucagon rises.[60] The fall in plasma glucose level is greater in female than in male subjects.[61] Merimee and Tyson[61] noted a mean plasma level of glucose of 47.8 ± 2.9 mg per dl in 12 nonobese women who fasted for 72 hours compared with 66.4 ± 2.9 mg per dl in 12 nonobese men who also fasted for 72 hours. The reason for this sex difference is not clear. Relative muscle compartment size[62] (women have a lower lean body mass-to-adipose ratio) and estrogen and progesterone modulation of tissue uptake[63] and use of glucose have been suggested as possible explanations. Women are also known to become ketotic more rapidly than men

during fasting, and ketosis appears to decrease gluconeogenesis, thereby indirectly affecting plasma glucose levels.

Protein Conversion

Nitrogen Balance

In our subject, total urinary excretion of nitrogen fell from 10 to 12 grams per day in the first week to 5 to 7 grams per day after the third week (Figure 5). In prolonged starvation survival depends on conserving protein stores while energy for essential metabolic functions is maintained. Evidence that protein catabolism is reduced with continued fasting is reflected by the decrease in total urinary excretion of nitrogen. As expected, the urinary nitrogen excretion in our subject was somewhat greater than the losses of 3 to 6 grams per day observed in fasting obese persons.[64] Cerebral adaptation to ketone use lowers glucose requirements, thereby reducing the need for gluconeogenesis.[65] The fall in urea excretion (Figure 5) suggests decreased hepatic gluconeogenesis from amino acids.[64] In addition, the hyperketonemia of starvation may exert a direct inhibitory effect on gluconeogenesis. Sherwin and co-workers[59] found a reduction in serum alanine levels of 30 percent after one-hour infusions of β-hydroxybutyrate in obese persons who fasted for five to ten weeks (Figure 6).

Along with this fall in blood alanine level, total urinary nitrogen excretion decreased 30 percent. As discussed previously, alanine is the major amino acid gluconeogenic precursor during fasting. A reduction in alanine formation results in decreased gluconeogenesis and hence a decrease in protein catabolism. Thus it would appear that the hyperketonemia of starvation exerts a direct protein-sparing effect by reducing alanine release from muscle. Although the exact mechanism is not known, it has been suggested that ketones may directly inhibit the oxidation of branched chain amino acids in muscle, thereby stopping the synthesis of alanine and turning off the glucose-alanine cycle.[59]

Conversely, recent evidence indicates that alanine may inhibit ketone production directly, suggesting the presence of a ketone-alanine cycle.[66] The importance of substrate cycling in homeostatic control of intermediary metabolism has only recently been appreciated, and in the case of a ketone-alanine cycle further investigation to elucidate its full significance is required.

Also apparent in Figure 5 are the changes in urinary ammonia levels. Ammonia production and excretion increase steadily (maximal by day 10) under the stimulus of ketoacidosis.[64] As discussed earlier, the major obligate cation lost early in fasting (to compensate for the increased excretion of metabolically generated anions) is sodium. As fasting progresses, sodium conservation is

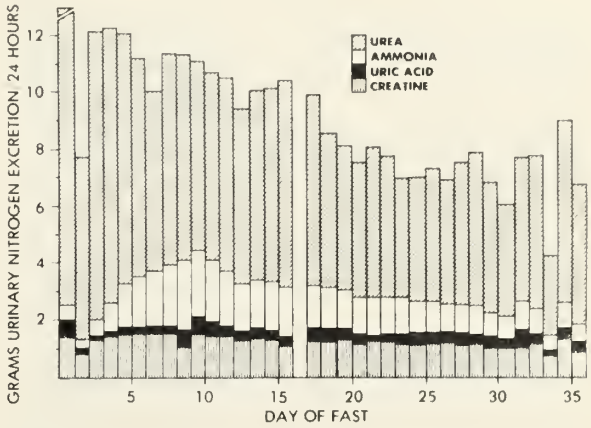

Figure 5.—Total urinary nitrogen excretion. Note the gradual increase and then decrease of urinary excretion of ammonia and the absolute reduction in total nitrogen excretion as fasting progresses.

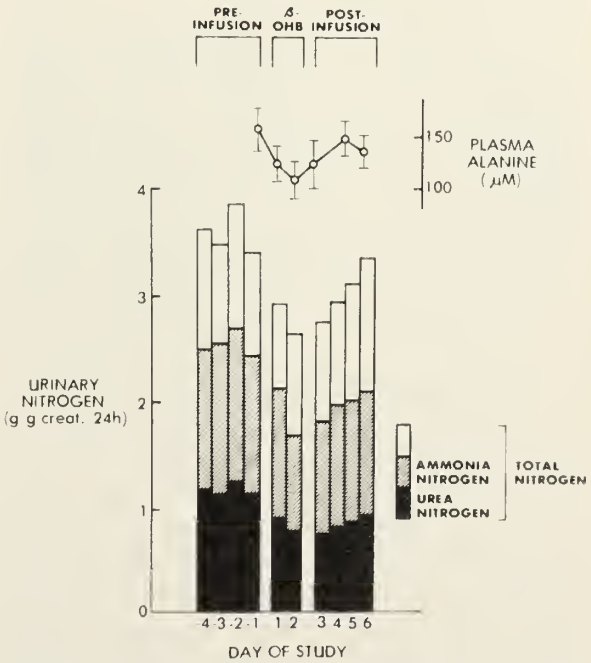

Figure 6.—The effect of an infusion of β-hydroxybutyrate (β-OHB) on urinary nitrogen excretion and plasma alanine concentration during prolonged (five to ten weeks) fasting. Infusions were for 12 hours (9 AM to 9 PM) on each of two consecutive days, and data presented are mean values for five subjects. Plasma alanine and urinary nitrogen levels fell significantly ($P<.025$) in response to the infusion (from Sherwin et al[59]).

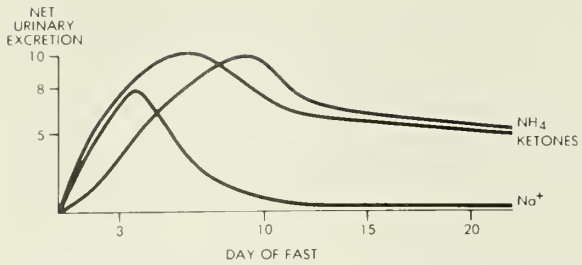

Figure 7.—A schematic of the relationship between ketonuria, ammoniuria and the natriuresis of fasting. Sodium (Na^+) losses decrease as ammonium (NH_4) becomes available as a cation to be excreted with ketones. Ketone losses decrease due to increased renal reabsorption; this is accompanied by a decreased ammonium excretion.

linked to increased ammonia production and excretion.[42,43] The relationship between ketonuria, ammoniuria and the natriuresis of fasting is diagramed in Figure 7.

Lipolysis and Ketogenesis

In our subject total lipid levels fell slightly whereas triglyceride levels rose (Table 3). Also, a pronounced increase in triglycerides was seen on refeeding as fuel stores were rapidly replenished in the hypercalorie state.

In the transition from a fed to a fasted state, fat stores are rapidly mobilized. Lipolysis, which is the hydrolysis of triglycerides to free fatty acids and glycerol, is stimulated by a fall in insulin levels and a rise in glucagon levels. In the postabsorptive state free fatty acids are mobilized at the rate of about 7 grams per hour and are taken up by the liver at about 3 grams per hour where they are terminally oxidized to CO_2 (β-oxidation), partially oxidized to ketone bodies (ketogenesis) or resynthesized into triglycerides (lipogenesis).[30] The major ketone bodies are β-hydroxybutyrate and acetoacetate, which may rise 70-fold during prolonged fasting.[64] Regulation of ketogenesis is dependent on substrate availability (that is, free fatty acids) and transport into the hepatic or renal mitochondria where oxidation occurs. The enzyme responsible for this transfer, carnitine acyltransferase, is indirectly stimulated by glucagon in the absence of insulin.[30] As fasting continues, increased cerebral use of ketone bodies occurs as greater ketonemia develops.[65,67] Serum levels of ketone bodies rise steadily during three to four weeks,[68] whereas lipolysis and ketogenesis are maximal by three days.[69] This discrepancy between increasing serum levels and stable production rates is explained by the decreased peripheral uptake and decreased renal excretion of ketones.[68] Muscle uptake of ketones falls by 75 percent from early to prolonged fasting as energy for muscle metabolism shifts from ketones to free fatty acids.[70] In addition to increasing plasma ketone levels, the increased reabsorption of ketones by the kidney has a nitrogen-sparing effect by decreasing the ammonia excretion required to titrate urinary ketone losses.[68] Thus, in addition to providing substrate, the ketonemia of starvation provides feedback inhibition of protein catabolism.

Sex Differences and Body Size in the Development of Fasting Ketosis

As early as 1931 differences during fasting between men and women have been shown.[71] It was not until the late 1950's, however, after Bloom[15] reintroduced fasting as a treatment of morbid obesity, that interest in and study of fasting metabolism became widespread. Rapid weight loss under medical supervision became a major incentive for prospective volunteers; as a result, most of the information collected during prolonged fasts during the past two decades is from studies with obese persons. Unfortunately, in these studies and in fasting studies with nonobese persons, the data generally were not analyzed for possible differences based on sex or body size. Not until 1974 was it recognized that there are differences in plasma glucose levels between fasting nonobese men and women,[61] and apparently the influence of sex and body size must be considered before interpreting any findings.

Deuel and Guliek[71] first reported that fasting ketosis develops more rapidly in women than in men. Also, serum free fatty acids and ketone levels increase at a greater rate in women than in men during fasting.[72,73] This sex difference, however, disappears with increasing body weight.[74,75] Maximal mobilization of free fatty acids occurs only at reduced levels of insulin. However, in obese persons both basal and fasting levels of insulin are raised.[64] Although insulin is known to be less sensitive in obese persons,[76] at least for its primary action, its secondary or antilipolytic effect could be a predominant factor in the reduced rate of lipolysis. In addition, little or no rise in growth hormone is seen after prolonged fasting in obese subjects[77-79]; this hyperinsulinemia and lower growth hormone level would be expected to make fat mobilization more difficult in an obese person. Conversely, growth hormone

levels in nonobese persons are raised during fasting,[79,80] and in the presence of lower insulin and higher glucagon levels lipolysis is enhanced. One might postulate that in a nonobese fasting person the stimulus for mobilization of free fatty acids and ketogenesis is greater due to lower plasma glucose, lower insulin, and elevated glucagon and growth hormone secretion.

Other sex differences include the glucagon level, which has been shown to be higher in nonobese fasting women than in men.[81] A role for glucagon in the explanation of the sex-based variation in fasting ketosis has been suggested.[81] As discussed earlier, ketosis has been shown to decrease the release of amino acid gluconeogenic precursors (especially alanine) from muscle and may represent another important control point in the regulation of intermediary substrate cycling. Merimee and associates[81] found lower but not statistically significant reductions in serum alanine levels between nonobese men and women after 24 and 48 hours. Their subjects, however, were chosen based on previous studies showing similar fasting insulin levels. They suggested that if women with lower fasting plasma glucose levels (and hence lower insulin production) are studied, a difference in the release of amino acid gluconeogenic precursors might be evident. Furthermore, if a decreased release of gluconeogenic precursors in fasting women is found, a lower plasma glucose level could be explained. Further investigation is necessary to resolve this issue.

Other explanations for the greater ketosis in fasting women include sex differences in body composition,[62] estrogen effects,[63] and differential use or conversion of free fatty acids to ketones.[62] The mobilization of fuel stores during fasting depends on the energy requirements and the hormonal milieu. Previous explanations may have oversimplified the role of certain hormones. A partial list of differences between men and women and lean and obese persons is shown in Table 4.

Hormonal Changes

The important roles of insulin and glucagon in the adaptation to fasting have already been discussed and have been reviewed extensively by others.[30] Other endocrine changes that also occur during fasting are as follows.

Growth Hormone

We observed a progressive rise in growth hormone level through day 26 followed by a significant fall thereafter with a return to baseline levels during realimentation (Table 3). Growth hormone plays a key role in protein, carbohydrate and fat metabolism. It also has known lipolytic effects[87] and may be diabetogenic in large doses or in smaller amounts in the absence of insulin.[88] Its secretion fluctuates widely during the day with a major increase during early sleep.[88] Other known stimuli to growth hormone secretion besides fasting include hypoglycemia, exercise, certain amino acids (for example, arginine and other

TABLE 4.—*Differences in Metabolism During Fasting Related to Sex and Body Size**

	Obese Subjects		*Nonobese Subjects*		
	Women	*Men*	*Women*	*Men*	*References*
Substrate					
Glucose	↓↓↓	↓↓	↓↓↓	↓	61,62,64,81
Free fatty acids	↑↑	↑	↑	↑	62,72,73,75,78,81
Ketones	↑↑	↑	↑	↑	62,71-75,78,81
Amino acids (especially alanine)	0†	0†	?	?	81
Hormones					
Insulin	↓↓	↓↓	↓	↓	61,62,64
Glucagon	↑↑‡	↑	↑	↑	55,62,81
Growth hormone	↑↑↑‡	↑↑	0	0	78-80,82
Miscellaneous					
Rate of weight loss	↓↓↓	↓↓↓	↓	↓↓	83-85
Total urinary nitrogen excretion	↓↓	↓↓	↓	↓	72,83,85
Total urinary mineral excretion (calcium, magnesium, phosphorus, sodium, potassium)	↑	↑	↑↑	↑↑	73,86

0 = no change
? = unknown

*Arrows indicate a relative quantitative change. This table represents a summary of data in an area that has not been adequately studied.
†Although no change was noted by Merimee et al,[81] it has been shown that infusions of β-hydroxybutyrate stimulating the hyperketonemia of fasting results in a decrease in amino acid gluconeogenic precursors, especially alanine[59]; on that basis some sex difference might be expected. Additional studies are necessary.
‡Basal growth hormone levels (after an overnight fast) are raised in women compared with men, but no significant increase occurred in women after 72 hours of fasting.[80]

TABLE 5.—*Serum Thyroxine (T_4), Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) Before, During and After Fasting*

Day of Study	*T_4 (μg/dl)*	*LH (mIU/ml)*	*FSH (mIU/ml)*
Before Fasting			
	5.9	47	6
Fasting			
5	6.5	20	6
12	6.4	16	4
19	5.5	12	3
26	5.3	10	3
33	3.9	9	2
36	4.9	10	2
After Fasting			
7	2.6	8	3
12	4.4	..	..
Normal Range	4.5-12.5	6-30	5-25

mIU = milli-international units.

basic amino acids), catecholamines, stress (for example, fever or surgical procedures) and certain drugs (for example, L-dopa, vasopressin).[89]

In addition, the secretory pattern of growth hormone in response to provocative stimuli appears to vary among obese and nonobese persons.[79,90] In obese persons, little or no rise in growth hormone has been reported after fasting from 14 to 38 days.[91,77,78] Conversely, in other studies mean serum growth hormone values rose within three days and then fell in nonobese persons during fasting from three to ten days.[60,80,91] The progressive rise in the level of growth hormone beyond day 10 is surprising in view of the previous reports, but we are unaware of growth hormone determinations in nonobese persons fasting beyond ten days.

In an interesting study by Merimee and coworkers,[92] six normal and ten growth hormone-deficient dwarfs fasted for six days. Four of the growth hormone-deficient dwarfs received growth hormone replacement during the fasting period. Glucose levels fell 15 mg per dl in the normal and growth hormone-treated dwarfs but fell 50 mg per dl in the untreated dwarfs. The insulin level also fell whereas free fatty acid and serum ketone concentrations increased to a greater degree in the untreated dwarfs compared with the normal and treated dwarfs. Although growth hormone may have a lipolytic effect, these studies suggest that it is not primary. The higher level of free fatty acids and ketones noted in the untreated dwarfs was probably related to the lower plasma insulin levels. Nevertheless, it is apparent that glucose homeostasis during fasting is dependent in part on the presence of growth hormone.[93]

Thyroid Hormone

Values for serum thyroxine (T_4) in our subject over the fasting and realimentation periods are shown in Table 5. The T_4 level showed only a slight decline from the early to the late fasting periods, and remained depressed at the end of the first week of realimentation. Serum triiodothyronine (T_3), thyrotropin (thyroid-stimulating hormone, or TSH) and reverse T_3 were not measured.

In starvation and fasting states, T_4 has been reported to be unchanged,[94] increased slightly[95] or decreased slightly,[91] whereas serum T_3 falls dramatically.[95] Spaulding and colleagues[96] and Portnay and associates[95] showed a reduction of free T_3 levels by approximately 50 percent in persons who fasted for one to four weeks. This reduction in T_3 is due to an increased production of reverse T_3, an inactive metabolite, and to a lesser extent to a decrease in the peripheral conversion of T_4 to T_3.[97] It also appears to be related to the carbohydrate content of the diet.[96,98] Spaulding and co-workers[96] were able to prevent the fall of T_3 levels in persons fed hypocalorie diets containing at least 50 grams of carbohydrate but not in the same persons fed hypocalorie protein, fat or mixed protein-fat diets.

Despite the fall in T_3 levels, clinical hypothyroidism does not develop. Thyrotropin values do not rise, as might be expected in primary thyroid dysfunction; in fact, basal TSH concentrations may decrease in short-term fasting[98] or remain unchanged in prolonged (more than three weeks) fasting.[95] In addition, TSH response to thyrotropin-releasing hormone infusions may be blunted[98,99] or unchanged.[95]

The diversion of T_4 metabolism from T_3 to reverse T_3 is an adaptive mechanism that reduces caloric requirements by lowering the basal metabolic rate and thereby indirectly reducing the need for glucose derived from protein catabolism. The protein-sparing effect of this physiologic fall in T_3 has been well studied.[94,100] In obese persons given physiologic doses of exogenous T_3 to prevent the normal fall of the T_3 level during fasting, a significant increase in total urinary nitrogen excretion has been found.[100] No change in total urinary excretion of nitrogen occurs in persons receiving normal nutrition given similar doses.[100] In another study of lean fasting men given 5 mg

of T_3 every 3 hours for 80 hours to maintain normal serum T_3 levels, excretion of urea increased 9.1 percent from earlier fasting control values.[94] Another marker of protein catabolism, 3-methylhistidine, a component of actin and myosin that cannot be used again for protein synthesis and is excreted almost entirely in the urine, has been shown to increase paralleling nitrogen losses in fasting persons in response to exogenously administered T_3.[100,101]

In persons given larger doses of T_3 (150 mg every 12 hours) for 72 hours before and during a 72-hour fast, excretion of urea increased 2 to 2½ times whereas creatinine excretion increased six to nine times above control levels.[102] In addition, plasma glucose, free fatty acids, serum ketones and urinary ketone excretion increased significantly, suggesting accelerated gluconeogenesis, lipolysis, β-oxidation and ketogenesis in response to exogenous T_3 in a fasting but not a fed state.[101]

In anorexia nervosa, as in fasting and other malnourished states, T_4 and T_3 levels are reduced and TSH levels are unchanged, whereas reverse T_3 values may be increased.[103-105] In six patients with anorexia nervosa in a study by Moshang and coworkers,[103] T_4 levels were reduced slightly whereas T_3 levels were 50 percent lower than the levels of normal control subjects. The basal TSH concentration and response to thyrotropin-releasing hormone were not different in anorexic patients when compared with normal control subjects.

Gonadotropins

Serum luteinizing hormone and follicle-stimulating hormone (FSH) values are shown in Table 5. Both hormone levels fell during fasting and remained low after the first week of realimentation.

We are unaware of comparative findings in nonobese men during a similar period. Many of the data on gonadotropin response to weight loss comes from studies of patients with anorexia nervosa and self-imposed nonpsychopathologic weight loss or simple weight loss. Boyar and colleagues[106] studied the secretory pattern of luteinizing hormone in nine patients with anorexia nervosa by measuring luteinizing hormone levels at 20-minute intervals for 24 hours. They found a luteinizing hormone secretory pattern resembling that of prepubertal and pubertal children that reverted to a "mature" pattern with weight gain. More recent studies have reported low levels of serum luteinizing hormone and FSH[104] in patients with anorexia nervosa with a delayed response to exogenous luteinizing hormone-releasing hormone.[107-109] A delayed response to luteinizing hormone-releasing hormone has also been noted in simple weight loss, but the response was intermediate in extent between that in anorexia nervosa patients and normal persons.[109] The response to luteinizing hormone-releasing hormone in both conditions of weight loss returns to normal[110] or becomes supranormal[108] with weight gain, but resumption of menstruation in anorexia nervosa may not occur immediately, suggesting that other factors (most likely psychologic) are also involved.[105] Thus it appears that hypothalamic dysfunction in patients with anorexia nervosa and to a lesser degree in patients who have undergone nonpsychopathologic weight loss is related to the extent of weight loss.

Frisch and McArthur[111] postulated that a minimal weight-for-height ratio representing a critical

TABLE 6.—*Serum Sodium (Na^+), Potassium (K^+), Magnesium (Mg^{++}), Calcium (Ca^{++}) Phosphorus (P), Zinc (Zn) and Uric Acid Levels Before, During and After Fasting*

Day of Study	*Na^+ (mEq/liter)*	*K^+ (mEq/liter)*	*Mg^{++} (mg/dl)*	*Ca^{++} (mg/dl)*	*P (mg/dl)*	*Zn (μg/dl)*	*Uric acid (mg/dl)*
Before Fasting	138	4.6	1.7	10.3	3.6	104	5.5
Fasting							
5	134	4.8	1.4	9.6	2.6	255	11.2
12	132	3.9	1.4	10.1	2.6	...	12.6
19	131	4.1	1.2	10.0	3.0	342	12.5
26	130	4.7	1.5	10.5	2.8	307	10.5
33	134	4.8	1.5	10.2	3.8	284	8.4
36	122	...	1.6	9.8	3.0	364	8.0
After Fasting							
7	136	5.3	1.6	9.1	3.0	117	2.0
12	139	4.3	...	9.4	4.0	...	3.5
Normal Range	(134-146)	(3.5-5.3)	(1.5-2.9)	(8.8-10.8)	(2.0-4.7)	(80-120)	(2.5-8.5)

adipose store must be attained before onset and maintenance of normal menstrual cycles. As with anorexia nervosa, simple weight loss and protracted strenuous exercise all deplete adipose stores, resulting in menstrual irregularities. Amenorrhea, oligomenorrhea and anovulatory cycles have been reported in long distance runners,[112,113] ballet dancers,[114] and female participants in strenuous sports,[115] as well as in cases of anorexia nervosa and simple weight loss. Because infant survival depends on birth weight, which is affected by maternal weight both before and during pregnancy, successful reproduction including lactation depends on adequate maternal energy stores. Teleologically, this represents an adaptive mechanism that limits reproduction when body energy stores are suboptimal.[116]

Whether or not the changes in luteinizing hormone or FSH levels that we observed are consistent findings in fasting nonobese men and are analogous to the changes seen in women needs to be studied further. Changes commonly seen in men during periods of reduced caloric intake include loss of libido, decreased volume of prostatic fluid, and decreased sperm number and motility.[13]

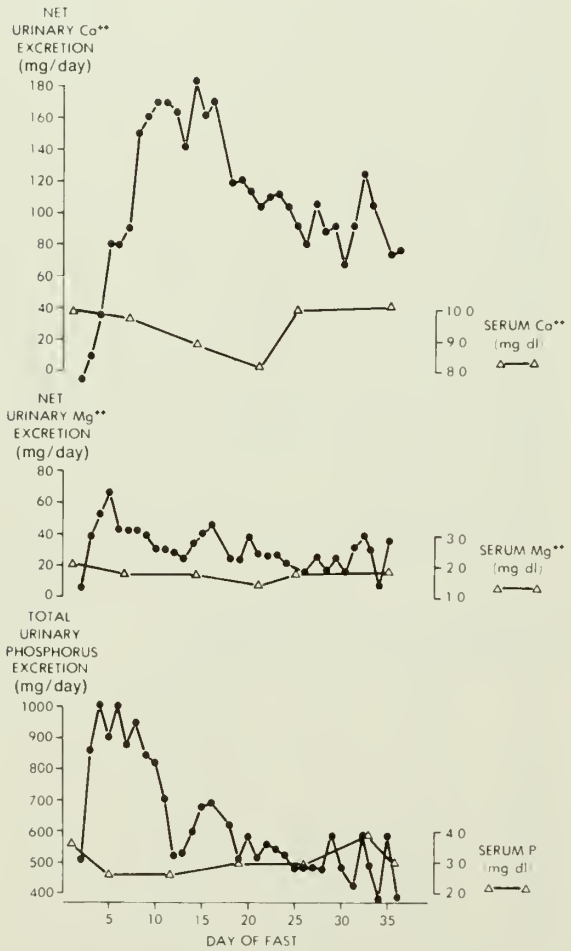

Figure 8.—Net urinary calcium (Ca^{++}) and magnesium (Mg^{++}) excretion and total urinary phosphorus (P) excretion over the fasting period. Serum levels are shown on the right.

Mineral Changes

Potassium

Serum potassium levels remained essentially unchanged in our subject (Table 6), but there was a net total urinary loss of potassium of 37.6 mEq per day for the first ten days or 729.6 mEq over the entire 36-day fast. Serum potassium levels may decline slightly, but rarely fall below 3.0 mEq per liter even after two or more months of unsupplemented fasting.[86] Urinary potassium losses observed by others[86] in the early fasting period (first ten days) were similarly large, averaging 33 to 41 mEq per day in lean persons. Consolazio and associates[117] noted a mean loss of 39.1 mEq per day during a ten-day fast in six normal men. Benedict[9] reported a similar pattern of urinary potassium excretion with an average daily loss of 19.9 mEq per day in a 31-day fast. In obese persons fasting a month or longer, potassium losses are less than half those of lean persons.[86] Because net potassium loss is primarily from lean tissue, these decreased losses in obese persons may represent more efficient protein sparing as fat stores are mobilized.

Magnesium

Serum magnesium levels were remarkably stable, whereas urinary excretion of magnesium increased over the first five days and then fell gradually to approximately 2 to 3 mEq per day by the end of the fasting period (Figure 8). Total net urinary magnesium excretion equaled 2.6 mEq per day or 93.6 mEq over the 36-day fast.

Magnesium deficiency in persons with protein-calorie malnutrition is well recognized.[118-120] Signs and symptoms compatible with magnesium deficiency include weakness, emaciation, anorexia, insomnia, hyperirritability, atrophic skin changes and hypocalcemia.[121] Electrocardiographic changes include nodal or sinus tachycardia and flat or inverted T waves in the lateral precordial leads.[121] In children with severe protein-calorie malnutrition and clinical signs and symptoms of magnesium deficiency, magnesium-supplemented realimentation results in dramatic and rapid improvement in

serial electrocardiograms along with a return of appetite, resumption of a normal sleep pattern and stabilization of vital signs.[121]

In cases of acute starvation, evidence of magnesium deficiency generally is not seen. In obese persons fasting up to 60 days, serum levels may be slightly increased, decreased or remain the same.[86] Consolazio and colleagues[117] observed a pattern of urinary magnesium excretion during fasting that was similar to our subject's. Benedict[9] reported an average magnesium loss of 6.0 mEq per day over a 31-day fast. Gamble and co-workers[122] noted a net total loss of 51.2 mEq of magnesium after a 15-day fast of nonobese epileptic children, whereas after 15 days in our study net total magnesium loss equaled 50.1 mEq. Urinary magnesium excretion is somewhat higher in obese persons, averaging 13 mEq per day over the first seven days, thereafter receding to a stable minimum excretion of 7 to 10 mEq per day.[86]

Calcium

In our subject, serum calcium levels fell slightly (Figure 8) by the third week but returned toward the baseline level by the end of the fasting period. Serum calcium levels have not been reported to be significantly altered by fasting, probably due to the large bony reserves. Urinary excretion of calcium increased steadily through the second week of fasting and then fell gradually before stabilizing at around 4 to 5 mEq per day (Figure 8). The average net urinary calcium excretion for the 36-day fast was 5.3 mEq per day or 190.8 mEq.

Calcium losses during fasting vary. The calcium loss in our subject compared quite favorably with findings in nonobese fasting persons.[9,117,122] Consolazio and co-workers[117] reported a 6.4 mEq daily loss during a ten-day fast of nonobese men that was comparable with a loss in our study of 5.3 mEq per day. Benedict[9] noted a net urinary calcium loss of 10.9 mEq per day over the 31-day fast of nonobese Mr. L. Gamble and colleagues[122] reported a total urinary loss of calcium of 51.2 mEq at day 15 in four epileptic children, which was comparable with the 50.1 mEq loss over the same time period in our subject. In obese subjects, Drenick[86] reported total urinary losses between 550 and 900 mEq (11 to 18 mEq per day) during a 50-day fasting period with a pattern of excretion similar to that of magnesium. In another study of three obese women, net calcium excretion during fasting periods of 12, 20 and 24 days amounted to total losses of 3.5, 10.2 and 14.7 mEq per day, respectively.[123]

The source of this calcium is presumed to be bone, though actual analysis of bone for calcium content change during fasting has not been carried out in humans.[86] Osteoporosis with hypercalciuria is a well-documented consequence of immobilization.[124] Therefore, considerable variation in calcium losses might occur between physically active versus inactive fasting persons. Our subject was fully ambulatory throughout the fasting period, as are most persons studied during fasting.

Phosphorus

Serum phosphorus levels and total urinary phosphorus excretion in our subject are shown in Figure 8. Serum phosphorus levels did not change significantly. Peak urinary phosphorus losses occurred on days 4 through 6, decreasing steadily thereafter to approximately 0.5 gram per day by the end of the fast.

Phosphate losses during fasting in obese persons are initially quite high, up to 80 mEq per day, before falling to average daily losses of 20 to 30 mEq after 15 to 20 days.[86] Rapoport and associates[125] noted similar losses closely paralleling the curve of titratable urinary acidity and suggested that phosphate might play a role in buffering the metabolic acidosis of starvation.

Because sufficient quantities of phosphorus are readily available in almost all foodstuffs, dietary phosphorus deficiency under normal conditions is uncommon in humans.[126] However, a phosphorus-depletion syndrome from prolonged antacid therapy, chronic alcoholism, diabetic ketoacidosis, thermal burns, hyperalimentation or severe respiratory alkalosis has been described.[126-128]

Zinc

Serum zinc levels in our patient are shown in Table 6. A prompt and sustained increase was noted throughout the fasting period. With alimentation, serum levels fell to within the normal range. Urinary excretion of zinc was not measured in our subject.

Few studies of zinc metabolism during fasting have been reported. We are unaware of any such studies in nonobese persons fasting for prolonged periods. Spencer and co-workers[129] reported a twofold increase in urinary zinc excretion in the first six days of total fasting in an obese person. Thereafter, zinc excretion remained high, averaging a 4.6 mg per day loss throughout a 60-day

starvation period. Despite these large urinary losses, serum zinc levels rose slightly, but not to the extent observed by us. The source of this zinc is presumed to be from tissue catabolism and bone resorption.

Zinc is an essential cofactor or forms a metalloenzyme for more than 70 known enzymes.[130,131] It plays a role in protein, carbohydrate, lipid, and nucleic acid synthesis and degradation. An excellent review of zinc metabolism and its clinical implications has been published recently.[132]

Zinc deficiency was first suspected in 1961 by Prasad,[133] who reported a syndrome of dwarfism, hypogonadism, hepatosplenomegaly and parakeratosis in men from Iran. Zinc-deficient states have since been reported in a variety of clinical conditions. Zinc deficiency has been associated with abnormal growth, abnormal sexual maturation and function, anorexia, hypogeusesthesia, dysgeusia, hyposmia, dysosmia and impaired wound healing.[132,133] Total body zinc stores are about 1.5 to 2.5 grams with about 60 percent found in muscle and 30 percent found in bone.[132,134] Under normal conditions, these reserves are not thought to be readily available, thereby necessitating a minimum daily requirement. For adults this is about 15 mg per day, increasing to 20 to 25 mg per day during pregnancy or lactation.[132]

Uric Acid

In our subject, serum uric acid levels rose rapidly over the first two weeks, stabilized during the third week and fell thereafter to the upper limit of the normal range (Table 6). Urinary excretion of uric acid averaged 400 mg per day after the first week of fasting and changed very little thereafter (Figure 5). Most other studies have reported urinary uric acid excretion to decrease with fasting.[135,136] This fall in serum uric acid that occurred in our patient while renal excretion was stable may represent decreased uric acid production as protein-sparing mechanisms are activated later in fasting.

Hyperuricemia is a well-established consequence of fasting.[136-138] In a nonobese person studied in the last two days of a 45-day fast, a serum uric acid level of 9.0 mg per dl (normal 3 to 4 mg per dl) was recorded.[11] We are otherwise unaware of serum uric acid levels measured in nonobese persons during prolonged fasting. In another study of obese patients who fasted for up to four months, serum levels of uric acid increased progressively for the first 15 to 20 days to levels of 12 to 18 mg per dl (normal in men, 4.0 to 8.5 mg per dl) reaching an average maximum of 21.8 mg per dl as fasting extended beyond two months.[139]

Explanations for the hyperuricemia of fasting include increased production[140] or decreased excretion due to decreased glomerular filtration rate,[136] altered renal tubular transport systems[136] or ketoacidosis.[141] Uric acid and keto acids are thought to compete for renal tubular transport sites. Infusions of β-hydroxybutyrate to simulate the ketonemia of starvation have been shown to produce a pronounced renal retention of uric acid.[141,142] Acute episodes of gouty arthritis and urate nephrolithiasis with subsequent renal insufficiency have also been reported.[139,142] Probenecid and allopurinol have been used to control the hyperuricemia of fasting and prevent these complications,[143] but were not used in our study.

Psychologic and Neurologic Effects

Our subject remained lucid throughout the fast and maintained a rigorous schedule of daily meetings, conferences and worship while keeping a detailed journal of activity and subjective response to physical changes. Appetite was noted to diminish, but total anorexia did not develop. The sight and smell of food remained subjectively pleasant.

In conventional short-term calorie-deficient diets, persistent hunger has been a major obstacle to patient compliance. However, loss of appetite (after one to four days) along with a sense of well-being has been reported frequently in persons on short total fasts for weight reduction.[15-17,144] Others[18] have reported euphoria without total anorexia. Ketosis, which develops rapidly during fasting, was commonly believed to be responsible for the anorexia.[16] More recently, β-endorphin, an endogenous opiate that has been linked to feeding regulation and satiety, has been postulated to be involved in this physiologic adaptation to fasting.[145]

The sense of well-being that may occur during short-term total fasting is in contradistinction to that seen during prolonged periods of semistarvation when mental lethargy, apathy and irritability are common.[13,33] To explain the euphoria, Bloom[15] postulated that accumulation of acetoacetic acid produces a mild intoxication similar to ethanol. Phillips[146] from studies in animals speculated that the accumulation of isopropyl alcohol in neural tissue might be responsible for fasting-induced religious, mystical or hallucinatory ex-

periences. One must also consider the positive psychologic benefits of significant daily weight loss in persons who have had lifelong histories of obesity previously refractory to any treatment.

Electroencephalographic studies in fasting persons have been limited. Owen and associates[60] reported no change in the findings on electroencephalograms of three obese persons who fasted for 38 to 41 days. In patients who fasted for psychosomatic disorders, fast-wave activity on electroencephalograms was reported to increase.[147] In studies of children suffering from kwashiorkor, electroencephalographic tracings showed abnormal slow-wave frequencies[148] or a high incidence of abnormal tracings in the temporal lobe.[149] In both studies a return of the electroencephalographic findings toward normal was reported with nutritional rehabilitation.

In other types of dieting, including liquid protein and protein-sparing modified fasting, anorexia is purported to be a prominent feature.[150,151] In a study of patients with Prader-Willi obesity who fasted on a protein-sparing hypocaloric regimen, the high degree of outpatient compliance obtained in these mentally deficient patients, who do not normally experience satiety, was believed to be due to an appetite-suppressant effect of the ketogenic diet regimen.[151]

Medical Complications of Prolonged Fasting

Complications reported during prolonged fasting for weight reduction are summarized in Table 7. Although prolonged fasting is generally well tolerated with few and relatively minor complications,[152] several reports of death after or during total fasting have appeared.[153,157-161] In addition to morbid obesity, two of six reported fatal cases had severe prefast symptoms of congestive heart failure (which initially improved with fasting) and one had focal stenosis of the coronary arteries at autopsy.[157,160] In another case a small bowel obstruction developed in the fasting person and death from complications occurred on the 13th day.[153] An abrupt onset of renal failure followed by death in another patient after 14 days of a total fast has been reported; chronic glomerulonephritis was found at autopsy.[161] In the sixth fatal case, the patient, who otherwise was in good health, had been given small amounts of protein supplements (essential amino acids) for 103 days of a 210-day fast, but died of intractable ventricular dysrhythmias on the eighth day of realimentation.[158] In this case, as is common in deaths of patients while on liquid protein fasts,[162] an otherwise unexplained prolongation of the QT interval was reported along with gross fragmentation of myocardial fibrils at necropsy. Although the cause of the dysrhythmias in these patients is unknown, perhaps this case represents the first reported though unrecognized death during protein-supplemented fasting.

TABLE 7.—*Complications During Prolonged Acaloric Fasting*

Complication	*References*
Nonfatal	
Headaches	15-18,152,153
Light-headedness	16,18,152
Nausea	15,16,144,152
Abdominal pain	153
Weakness	16,152,154
Cramps	86,152
Orthostatic hypotension	17,152,153
Acute gout	17,139,152
Urate nephrolithiasis	139
Renal insufficiency	139
Oliguria	18,144,152,153
Edema	18
Atrial flutter	152
Anemia	17,144
Amenorrhea	13,111
Alopecia	154
Porphyria	155
Parotitis	18
Polyneuritis	154,156
Vitamin deficiency	17,154
Fatal	
Intractable ventricular arrhythmia	157-159
Lactic acidosis	160
Small bowel obstruction with complications	153
Renal failure	161

Liquid protein diets, recently promoted heavily in the lay press[160] for weight reduction, are now known to be associated with serious complications including intractable ventricular dysrhythmias and sudden death.[163-165] Isner and colleagues[165] reviewed findings on 17 unexpected deaths in otherwise healthy obese persons using liquid protein diets. In all of nine patients for whom adequate electrocardiographic information was available, the QT interval was prolonged. Seven of the cases did not have the usual causes of QT interval prolongation—that is, hypocalcemia, hypomagnesemia, drugs or congenital anomaly. In another study of three persons with no previous history of cardiac disease who were on a liquid protein-fasting regimen, the QT intervals were prolonged, the ST segments and T waves were abnormal, and intermittent syncopal episodes due to ventricular tachycardia and ventricular fibrillation occurred for up to three months after discontinua-

tion of the diet.[166] All patients had electrocardiographic features of atypical ventricular tachycardia (torsades de pointes*); two of the patients died.[166] These studies suggest a causal relationship between liquid protein diets and delayed repolarization (prolonged QT interval), serious ventricular arrhythmias and risk of sudden death.

In an effort to assess the dysrhythmogenicity of liquid protein diets, six obese patients were given 300 kcal per day of a commercially prepared liquid protein hydrolysate for 40 days and were observed weekly with 12-lead electrocardiographic and 24-hour Holter monitoring.[167] No abnormalities were seen using standard 12-lead electrocardiographic monitoring in any patient before, during or after the fasting period. However, with 24-hour Holter monitoring, persistent and multiple ventricular dysrhythmias occurred in three of six patients after the tenth day of supplemented fasting. These dysrhythmias were noted to increase in frequency and complexity as the fasting period progressed. After resumption of normal diet, no further disturbances were seen with either standard 12-lead electrocardiograms or Holter monitoring in any of the patients. Although these findings are intriguing, unfortunately no control group was examined nor are there available comparative studies of Holter monitoring in persons undergoing other forms of dietary restriction such as total fasts, protein-sparing modified fasts or hypocaloric mixed diets. Although the cause of the life-threatening dysrhythmias seen in patients on protein diets is unknown, deficiencies of trace elements,[168,169] micronutrients[170] and essential amino acids,[171] as well as electrolyte disturbances[172,173] and biologically poor protein sources,[174,175] have all been suggested.

Summary

Early in fasting, weight loss is rapid, averaging 0.9 kg per day during the first week and slowing to 0.3 kg per day by the third week. During the period of rapid weight loss, there is significant negative sodium balance, probably due to losses of the sodium salts of keto acids in the urine. As mild starvation ketoacidosis develops, ammonia production is stimulated, providing ammonium for excretion with keto acids and thus sparing sodium loss. This leads to a decrease in the rate of weight loss. Carbohydrate-free fasts tend to cause orthostatic hypotension due to the sodium losses plus a degree of autonomic insufficiency. Other physical features such as the amplitude and axis on the electrocardiogram change, probably reflecting loss of cardiac mass, and bradycardia develops.

The early days of fasting are characterized metabolically by a high rate of gluconeogenesis, chiefly with the use of amino acids, especially alanine, as substrates. The stimulus for gluconeogenesis appears to be decreased insulin production and increased glucagon. As fasting continues, progressive ketosis develops due to mobilization and oxidation of fatty acids. At higher blood levels of ketones, the brain is able to use ketones as a primary energy source, thereby decreasing the need for gluconeogenesis. The specific feedback is probably by ketones on release of alanine from muscle. The ketotic phase of fasting is then associated with protein sparing. Lean persons become ketotic earlier than obese persons, and women become ketotic more rapidly than men.

Other hormonal changes occur. Serum levels of T_3 promptly fall with a reciprocal rise in reverse T_3, which contributes to protein sparing. Changes in the blood level of growth hormone during fasting are varied and may differ depending on whether the person is obese or nonobese. Changes in the blood level of gonadotropin are not well characterized; luteinizing hormone and FSH levels fall, at least in the patient reported herein.

Potassium losses decrease after ten days of fasting though some losses persist. Magnesium calcium and phosphorous losses are minimal after the first week.

Changes in trace metal balance are poorly defined. Serum zinc levels rose through the fasting period in the patient reported herein, but the significance of this change is unknown.

Hyperuricemia occurs in fasting obese persons and also occurred in our nonobese subject. This is probably due to increased production of uric acid from tissue catabolism and decreased urinary excretion of uric acid from competitive inhibition of tubular uric acid secretion.

The subjective psychologic effects of fasting may produce a sense of well-being or euphoria. Neurologically, there is evidence that ketosis may increase seizure thresholds in patients with epilepsy. Electroencephalograms in chronic protein-calorie malnutrition show diffuse slowing and abnormal temporal lobe tracings.

*Torsades de pointes means "twisting of the points" and is believed to represent an especially malignant form of ventricular tachycardia characteristically seen in association with a prolonged QT interval in which polarity of ventricular complexes swings between the positive and the negative directions.

Rare medical complications of short-term fasting include gout, urate nephrolithiasis, postural hypotension and cardiac dysrhythmias. The particular association of liquid protein-supplemented fasting and sudden cardiac death is well reported, though the mechanism is still unknown.

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Refer to: Golden J: *Pneumocystis* lung disease in homosexual men —Medical Staff Conference, University of California, San Francisco. West J Med 1982 Nov; 137:400-407

Pneumocystis Lung Disease in Homosexual Men

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. SMITH:* *This Medical Staff Conference will be concerned with* Pneumocystis *lung disease in homosexual men. Dr. Jeffrey Golden will make the presentation.*

DR. GOLDEN:† In discussing *Pneumocystis carinii* pneumonia among gay men, I will concentrate on our experience here at the University of California and share with you what we are learning from our patients. Thus far, more questions than answers have been generated. I view this discussion as an interim exercise. We hope to better understand this peculiar and deadly epidemic in the near future. Also, I intend to make some basic comments about interstitial lung disease which I hope will enlighten you on the general topic of restrictive lung disease as well as that consequent to infection with *P carinii*.

Presentation of a Case

Let me begin with a patient who presented with *P carinii* pneumonia a little more than a year ago. He was a 43-year-old homosexual man who had been admitted in April 1981 because of increasing shortness of breath for one month. During the previous five months he had fever and diarrhea. Two months before admission the diagnoses of amebiasis and giardiasis were made. One month before admission he was treated for syphilis. In the more distant past he had other diseases that we associate with his life-style, including hepatitis and shigellosis.

On physicial examination, he was febrile. His respiratory rate was increased and his chest was clear to auscultation. Blood gas determinations done while the patient was breathing room air showed oxygen partial pressure (Po_2) 66, and carbon dioxide partial pressure (Pco_2) 37 mm of mercury and pH 7.47. Findings on x-ray studies of the chest done at the time of admission showed bilateral lower lobe interstitial infiltrates.

Initially we expected this process to be a "walking pneumonia," with a viral or *Mycoplasma* cause. The next day his oxygen tension dropped to the low 50's. We decided to do bronchoscopy and were very surprised by the transbronchial lung biopsy result. Examination of the specimen after hematoxylin and eosin staining showed alveoli filled with a proteinaceous eosinophilic material. This type of alveolar filling process is pathognomonic of *P carinii*. Silver methenamine stain showed the cyst stage of *P carinii*.

The patient was given sulfamethoxazole and trimethoprim (Septra). After eight days of treat-

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ment his shortness of breath, hypoxia and radiographic abnormalities cleared. The administration of the medication was discontinued after eight days because of leukopenia and a rash. He was sent home without any medicines and did perfectly well for four months. He was able to return to work and to walk the hills of San Francisco without complaints of shortness of breath. We thought that was the last we had seen of this patient.

Four months after his initial episode of *P carinii* pneumonia, he was seen again with a one-week history of shortness of breath. Findings on the chest x-ray film done on admission again showed bilateral lower lobe diffuse interstitial disease (Figure 1). On repeat transbronchial biopsy the diagnosis of *P carinii* pneumonia was made. This process worsened and during the next two days adult respiratory distress syndrome developed. The patient was put in the intensive care unit and given positive end-expiratory pressure. For the next three weeks he had an unrelenting downhill course. We witnessed, incidentally, the development of cor pulmonale in a period of two weeks. When a pulmonary artery line was placed at the time of admission to the intensive care unit, his pulmonary artery pressures were found to be normal. Two weeks later, with normal arterial oxygen tension maintained while receiving supplemental oxygen, his pulmonary artery pressures were as high as 80/40 mm of mercury. This interstitial lung process destroyed enough vasculature to cause pulmonary vascular hypertension in two weeks. An esophageal echocardiogram corroborated the diagnosis of cor pulmonale as manifested by a large right atrium and right ventricle and a small, slit-like left ventricle.

He was treated with pentamidine because of a recurrent rash after two days of taking sulfamethoxazole and trimethoprim. Repeat bronchoscopy was required to help decide whether or not we should continue pentamidine administration after two and three weeks of therapy. A bronchoscopic lavage of the patient's airways through his endotracheal tube was positive for *Pneumocystis* even after three weeks of pentamidine administration, just before he died. This tells us two things. First, one can carry out bronchoscopy safely through an endotracheal tube with positive end-expiratory pressure. In this context of a critically ill patient requiring positive airway pressure, we did a simple lavage. This is essentially a very expensive way of getting an induced sputum specimen. We

Figure 1.—X-ray film of the chest taken on the first day of patient's second University of California admission, showing classic interstitial infiltrates associated with *Pneumocystis carinii* pneumonia.

did not attempt a transbronchial biopsy for fear of causing a pneumothorax in the presence of positive airway pressure. Second, despite three weeks of pentamidine therapy, the *Pneumocystis* infection never cleared.

At autopsy small cysts were seen on the gross specimen of his lungs. The microscopic examination shows cysts alternating with areas of thickened, fibrotic alveolar walls. These cysts are also very evident on his last chest x-ray studies. We call these cysts "honeycombing." Honeycombing is the end stage of any severe interstitial process—asbestosis, sarcoidosis, scleroderma or *P carinii,* as in the case being discussed.

One month after the patient's initial episode of *P carinii* pneumonia, Dr. Arthur Ammann here at the University of California evaluated his immune status. At this time the patient was doing well and had normal immunoglobulin values. However, he was anergic on skin testing. His T-cell rosettes were decreased to 40 percent of his lymphocytes, instead of the expected 60 percent or greater. By monoclonal antibody assay the helper T cells were decreased to 7 percent; his suppressor T cells were increased to 65 percent, giving him a very low helper-to-suppressor cell ratio of 0.1. This ratio should be greater than 1.2. This low ratio implies almost no helper T-cell function. In addition, his lymphocytes did not function normally. When they were placed in mixed-lymphocyte culture or exposed to phytohemagglutinin, appropriate lymphocyte transformation was not evident. Even when he was well, this man had a severe quantitative and qualitative T-cell immunodeficiency. At this time we learned

that our colleagues in Los Angeles and New York were finding the same T-cell deficiency in homosexual patients who had *P carinii* pneumonia and Kaposi's sarcoma.

In summary, this first case was highly educational in that it taught us that gay men are at risk for immunosuppression. We also learned that bronchoscopy was sufficient to make a diagnosis without resorting to open-lung biopsy. This man did very well after a brief course of sulfamethoxazole and trimethoprim. Four months later, however, he had recurrent *P carinii* pneumonia that developed into adult respiratory distress from which he died despite pentamidine administration. As discussed, not only did he have interstitial fibrosis and honeycombing, the *P carinii* infection never cleared. Furthermore, cytomegalovirus was cultured from an autopsy lung specimen. The presence of concurrent cytomegalic infection has important implications in terms of the cause of this patient's state of severe immunosuppression.

Background

Let me say a word about the organism itself. *P carinii* was first discovered in 1909 by Chagas working with monkeys in Brazil.[1] He thought it was a developmental stage of *Trypanosoma cruzi*. The next year Carini found the organism in dogs and felt it was the schizogonal form of *Trypanosoma lewisi*. The first identification of this organism in human lungs was made by Van der Mear in the Netherlands in 1942. Vanek in 1952 established the causal relationship of *P carinii* and what was called interstitial plasma cell pneumonia of infants, which was epidemic during the socioeconomic collapse of Europe during and after World War II. In 1956 the first cases of *P carinii* pneumonia were found in this country.

The organism is a protozoon. It exists in two forms: a cyst form and a trophozoite form. One can only grow *Pneumocystis* in cell culture. It is very clear now that the disease is transmitted by inhalation. The trophozoite stage of *Pneumocystis* is inhaled and attaches to the alveolar lining epithelium. Pifer and co-workers[2] showed by phase-contrast microscopic observation of *P carinii* in chick epithelial lung culture that the trophozoite develops into a cyst form. The cyst matures and sporozoites develop within it. Subsequently, these sporozoites rupture out of the mature cysts and become trophozoites, and the cycle begins again.

P carinii is a ubiquitous organism. Studies at St. Jude's[3] showed that 80 percent of healthy subjects have significant titers to *P carinii* by the time they are 4 years old. This anti-*Pneumocystis* antibody is important in preventing disease from this ubiquitous infection. Masur and Jones[4] showed that minutes after adding anti-*Pneumocystis* antibody to a preparation containing living alveolar macrophages, *Pneumocystis* trophozoites are phagocytized by macrophages. By electron microscopy the trophozoite can be observed to degenerate immediately upon contacting the macrophage vacuole. Just as we have humoral antibodies to this organism, our lymphocytes are also sensitized to *Pneumocystis*. In randomly selected subjects studied by Herrod and colleagues,[5] 14 of 16 had lymphocytes that transformed spontaneously in the presence of *P carinii* cysts. Importantly, spontaneous transformation of lymphocytes by the *Pneumocystis* organism does not occur with naive umbilical cord blood. Evidently this protective mechanism must be acquired by prior inhalation of the organism.[6]

Despite a near universal exposure to this organism, our humoral and cellular immunity is very effective protection from disease. At St. Jude's, Perera and associates[6] have shown that *P carinii* pneumonia develops only in people with immunosuppressive diseases or receiving immunosuppressive therapy. Perhaps more interesting, looking at 301 consecutive autopsies, they found 40 patients who had *Pneumocystis* infection in their lungs but did not have pneumonia. Of these 40 patients with inapparent *Pneumocystis* infection, 39 were immunosuppressed. Similarly, Hamlin[7] found no *Pneumocystis* organisms in 245 consecutive autopsies done on patients dying without immunosuppressive diseases. Among 300 consecutive autopsies done on patients who had been severely immunosuppressed, however, *Pneumocystis* organisms in the lungs were identified in 14 (5 percent). Of these 14 cases, in only one was there associated pneumonia, the others having only inapparent infection. Presumably if these patients had lived longer or had more immunosuppressive chemotherapy, their inapparent infections may have developed into *Pneumocystis carinii* pneumonia. In fact, Perera's data do suggest that as one increases immunosuppressive chemotherapy in patients with leukemia, there exists a concomitant increase in the development of *P carinii* pneumonia. His leukemic patients given more immunosuppressive chemotherapy more frequently had clinical *Pneumocystis carinii* pneumonia and less frequently had inapparent

Figure 2.—Left, Normal chest x-ray study of a patient with an oxygen tension of 55 mm of mercury taken at the time a bronchoscopic examination that was positive for *Pneumocystis carinii* pneumonia. **Right,** X-ray film taken four days after initial normal film showing rapid progression of pneumonia.

Pneumocystis infection.[6] Clearly, it is the immune status that relates to development of diseases from this ubiquitous organism.

Clinical Features

What are the clinical features of *P carinii* pneumonia? There is a basic philosophical point to make here. The clinical features of *P carinii* pneumonia are consistent and found in almost every case; unfortunately they are nonspecific. Patients present with dyspnea, fever and often cough. Physical findings include an average temperature elevation of 38.8°C. One may or may not hear inspiratory rales on pulmonary auscultation. The most impressive feature of Walzer's series of 116 patients with *P carinii* pneumonia was the average oxygen tension of 46 mm of mercury.[8] In our series of patients we are finding cotton-wool exudates in the fundi, and this finding may be specific for *P carinii*. I should like to have Jim O'Donnell from our Department of Ophthalmology review some extraordinary eye findings in these patients.

Dr. O'Donnell:* We have been observing retinal cotton-wool spots in many gay male patients with unexplained immunosuppression. One such patient is a 34-year-old white man with a five-month history of fever, dry cough, dyspnea and weight loss. Funduscopic examination showed cotton-wool spots which existed in the presence of clear ocular media and normal retinal vessels. There was no evidence of ischemic retinal vascular disease such as hypertension or diabetes. These were actually cotton-wool spots by the jargon of ophthalmology, not exudates. They are infarctions in the nerve fiber layer which is on the superficial retina. The feathery edges are the nerve fiber layer itself. Despite therapy with sulfamethoxazole with trimethoprim as well as pentamidine, the patient died. At autopsy, light microscopy showed areas of nerve fiber layer degeneration and cytoid bodies. There was nonspecific staining with silver methenamine. Transmission electron microscopy, however, showed cyst forms of *Pneumocystis*. The *Pneumocystis* were seen in the ganglia and inner plexiform layers of the retina, adjacent to retinal vessels in the vicinity of the cotton-wool spots.

Extrapulmonary dissemination in *Pneumocystis* infection is rare, although the organism has been reported in lymph nodes, spleen, liver, peripheral blood, myocardium, stomach, small intestine, bone marrow, adrenal gland and thyroid. This is the first demonstration of *Pneumocystis* in the eye. It has not yet been found in the brain. The pathophysiology of this is obscure, but these organisms in the retina may cause focal nerve fiber layer infarctions which clinically manifest as the cotton-wool spots. There are many causes of cotton-wool spots, of course, and cotton-wool spots should not be regarded as pathognomonic for *Pneumocystis*. In terms of the current epidemic of unexplained immunosuppression in gay men, it is my clinical impression based on a limited number of patients that we are seeing cotton-wool spots in patients

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with *P carinii* pneumonia but we are not seeing them in patients with Kaposi's sarcoma. The clinical significance of this finding is that cotton-wool spots may be an important sign in patients with suspected *Pneumocystis*. The presence of cotton-wool spots in gay men without evidence of other ischemic retinal disease, such as diabetes or hypertension, should alert physicians to the possibility of *Pneumocystis* and the possibility of the immunosuppression syndrome. We are currently studying the correlation of these cotton-wool spots with the natural history of the disease and with the response to therapy.

DR. GOLDEN: We shall continue with other clinical aspects of *Pneumocystis carinii* pneumonia.

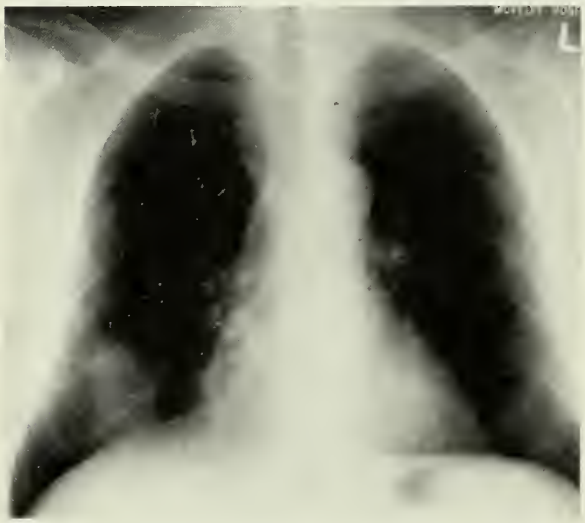

Figure 3.—X-ray study of the chest of a renal transplant patient with a localized infiltrate that proved to be *Pneumocystis carinii* on bronchoscopy.

Figure 4.—X-ray study of the chest showing diffuse infiltrates that proved to be pulmonary Kaposi's sarcoma on bronchoscopy and subsequent autopsy evaluation.

First we will mention the radiologic manifestations of this infection. As described for the first case, the usual radiologic presentation is diffuse interstitial infiltrates. There are exceptions to this classic radiologic pattern. For example, one of our patients came into the emergency room with an oxygen tension of 55 mm of mercury, complaining of two months of shortness of breath. Surprisingly, his admission chest x-ray film was entirely normal (Figure 2). Given his social history and oxygen tension, a bronchoscopy was done and a diagnosis of *Pneumocystis carinii* pneumonia was made despite normal chest x-ray studies. Another patient we have seen this past year presented with pneumonia and a localized nodular or mass-like infiltrate on an x-ray study of the chest (Figure 3) six months after a renal transplant. This localized lesion proved to *Pneumocystis carinii* pneumonia by bronchoscopy. Incidentally this patient was not gay. We now recognize that the radiologic presentation of *Pneumocystis carinii* has to be broadened to include even x-ray films that show no abnormalities and those showing localized abnormalities, not just diffuse interstitial disease.

How does one make the diagnosis of *Pneumocystis carinii* pneumonia? Uncommonly, the organism can be found in the sputum. Usually one has to rely on invasive techniques. We have found bronchoscopy to be 100 percent effective in diagnosing this disease. Open lung biopsy has been unnecessary. As of this conference, we have diagnosed *Pneumocystis carinii* pneumonia in seven gay patients with T-cell abnormalities and interstitial lung disease. We have been effective in ruling out *Pneumocystis carinii* pneumonia with bronchoscopy in four gay patients with T-cell abnormalities and interstitial lung disease. How do we know they are bronchoscopic true negatives? None of the four have gone on to show any changes consistent with *Pneumocystis carinii* pneumonia in months of follow-up. Instead, we have made bronchoscopic diagnosis of cytomegalovirus as the cause of their interstitial lung disease. In one gay man with known Kaposi's sarcoma, T-cell defects and radiologic evidence of interstitial disease (Figure 4), we diagnosed pulmonary Kaposi's sarcoma by transbronchial biopsy.

Cases Being Followed

One of the most basic questions that has arisen from this epidemic is how best to follow cases of

patients with previous *P carinii* pneumonia who are out of the hospital and doing well. As the initial case presentation illustrates, these patients must be observed for early signs of deterioration. At this point it is not clear which test—screening pulmonary function (lung volumes, airflow rates, diffusing capacity), exercise physiology, gallium lung scan, T-cell function and the like—should be done and how often. The answer to the related question of which test might be an effective screening device to detect the early manifestations of this type of pneumonia in the susceptible population also is not known.

We are now following in our outpatient department five homosexual patients with previous *Pneumocystis carinii* infection. I will present one of these cases as an example of how we are approaching the issue of appropriate follow-up. A 45-year-old gay man presented to the emergency room in October 1981 after two weeks of shortness of breath. On examination he was febrile and he had interstitial rales, thrush and an herpetic penile lesion. An x-ray study showed interstitial infiltrates and oxygen tension was 44 mm of mercury. After bronchoscopy the diagnosis of *Pneumocystis carinii* pneumonia was made. Despite intravenous administration of sulfamethoxazole with trimethoprim his pulmonary process progressed to adult respiratory distress syndrome. Given supplemental oxygen and positive end-expiratory pressure therapy, he began to improve slowly over a two-week period. He was discharged from the hospital two weeks later with dramatic clinical and radiologic clearing of his life-threatening pneumonia. Thinking back to our first patient who did well for four months only to die because of recurrent *Pneumocystis carinii* pneumonia, we wondered whether serial pulmonary function tests would be an effective way to follow his pulmonary status, especially in order to detect early signs of deterioration. His initial screening pulmonary function showed all three criteria of significant interstitial lung disease. First, all of his lung volumes were reduced, or "restricted," significantly below normal. Second, the diffusing capacity for carbon monoxide, a test for the intactness of the alveolar capillary bed, was reduced. Third, he had high airflow rates assessed by both forced expiratory volume in one second and maximal expiratory flow volume curves. High flow rates are typical of interstitial pulmonary disease and may result from high recoil pressure characteristic of stiff, noncompliant lungs. His small or restricted lung volumes, low diffusing capacity and high flow rates are consistent with his severe interstitial lung infection.

For the six months since discharge, he has been completely free of symptoms and has returned to work. He could not tolerate sulfamethoxazole with trimethoprim therapy because of a rash. He has been given monthly pooled immunoglobulin intravenously because we have detected humoral immunity dysfunction in terms of his response to pneumococcal vaccine. Finally, he has been sexually abstinent since discharge. His screening pulmonary function tests have shown slow but dramatic return to normal over this six month period. We are carefully observing his lung function to see if a subtle decrease in lung volumes or diffusing capacity might be a harbinger of recurrent *Pneumocystis carinii* pneumonia.

This patient has also had his pulmonary physiology assessed during exercise. We now know that a clear chest x-ray film[9] and so-called "normal" screening pulmonary function tests do not rule out the presence of significant interstitial lung disease. For this reason we undertake exercise pulmonary function testing to detect the presence of an underlying interstitial process in suspicious settings. Incidentally, it is now possible to show physiologic evidence of asbestosis with exercise testing in persons exposed to asbestos who complain of dyspnea on exertion but in whom screening pulmonary function test results are normal at rest.

This patient's exercise test was done on a bicycle ergometer with simultaneous collection of expired gases and arterial blood. In interstitial lung disease one expects an abnormal pattern of ventilation and gas exchange as the work load is progressively increased. Such patients hyperventilate primarily by increasing respiratory rate while maintaining small tidal volumes. This inappropriate hyperventilation is due to hypoxia, presence of a large dead space or, most important, a neural reflex arising in the distal lung parenchyma. In terms of gas exchange, a fall in oxygen tension and an increase in alveolar-arterial oxygen difference with the stress of exercise will develop in patients with interstitial lung disease even with normal resting arterial blood gas values. In contrast, in this patient results of an exercise test four months after his near fatal *Pneumocystis carinii* pneumonia were normal. His ventilation increased in a normal pattern with increasing exercise levels. Furthermore, his oxygen tension

was normal with each exercise level. Currently, this patient has normal pulmonary function at rest and with exercise. We will be conducting serial exercise tests with ear oximetry to follow this case. The development of abnormal hyperventilation with exercise may be an indicator of early clinical deterioration.

We are also evaluating gallium lung scans as another way to follow our patients with previous *Pneumocystis carinii* pneumonia. Findings on this patient's gallium lung scan now are normal and thus correlate with his normal exercise function. Two other similar outpatients still have positive gallium scans and repeat bronchoscopy in these two patients shows persistent *P carinii*. Thus our evaluation still shows *Pneumocystis carinii* pneumonia despite the absence of dyspnea on exertion. We shall continue to observe these patients using screening and exercise pulmonary function tests, gallium scans, bronchoscopy and T-cell functional studies to evaluate the effectiveness of treatment and early detection of clinical deterioration.

Summary of Cases

In summary, we have had eight gay patients present with *Pneumocystis carinii* infection. All the patients were white and male, and the age range was 31 to 46 years. Every patient's transbronchial biopsy specimen grew out cytomegalovirus. All had T-cell dysfunctions identical or similar to those of the first patient presented. The clinical courses of these patients have varied. Two patients had two episodes of pneumonia separated by many months. Both died after the second episode. One patient presented with mild shortness of breath and died after a rapid two-week downhill course. We now are observing five patients receiving various types of therapy, including administration of sulfamethoxazole with trimethoprim, immunoglobulin, thymosin and so forth. They are doing well clinically at this point.

Possible Causes

I would like to conclude with a discussion of the possible mechanisms of the immunosuppression that is central to this epidemic. First, we are not "reinventing the wheel"; this is a new phenomenon. True, *Pneumocystis carinii* and Kaposi's sarcoma are not new entities, but the immunosuppression in young gay men is certainly new. Why are these patients losing immune function? In a recent *Morbidity and Mortality Report* from the Centers for Disease Control, cases of 13 gay men with either Kaposi's sarcoma, *Pneumocystis* or both are presented.[10] Of these 13 patients, nine had recent, definite, direct sexual contact with other patients with either Kaposi's sarcoma or *Pneumocystis carinii* pneumonia before *Pneumocystis* pneumonia or Kaposi's sarcoma developed. Furthermore, of the six patients with Kaposi's sarcoma, in three the disease developed after sexual contact with patients known to have Kaposi's sarcoma.[10] This suggests that either there is something causal about their shared life-style or there is an infection being transmitted among members of this particular small cluster. What aspects of their shared life-style could contribute to immunosuppression? Obviously, drugs are a consideration. Marijuana, for example, has been shown to cause some T-cell problems in otherwise "normal" people.[11] Given the level of marijuana use in the San Francisco Bay Area, I think if marijuana were a significant cause of immunosuppression, the Immunology Clinic here at the University of California would have to meet in a football stadium. What are the other possibilities? Amyl nitrite is a drug of more recent popularity for its ability to heighten orgasm. In a recent article in *The Lancet,* researchers at the National Institute of Health reported that amyl nitrite, itself, can cause immunosuppression.[12] However, many of the patients in this series had "gay lymph node syndrome," or previous cytomegalovirus infection shown by serology, or both. This complicates interpretation of the effect of this drug on the immunosuppression syndrome.

If the recently reported clustering of cases in Southern California is confirmed, another possible cause of this epidemic immunosuppression is infection. In this context, a most likely candidate is cytomegalovirus. Here in San Francisco, Dr. W. Lawrence Drew showed that almost all homosexual men have positive serologies to cytomegalovirus. Furthermore, he also showed that 14 percent of gay men had this virus in their urine. This is based on only single urine samples. Perhaps if more than one sample were cultured, the virus might be isolated at an even higher frequency. No heterosexual patient in his series had a positive urine culture for cytomegalovirus.[13] In terms of the gay life-style, cytomegalovirus has particular relevance. First, we know that it can remain in the semen of an infected man for well over a year. This prolonged asymptomatic presence in semen undoubtedly relates to venereal transmission of the virus.[14] Furthermore, there are

significant immunologic sequelae due to cytomegalovirus infection. For example, it is the cause of the common mononucleosis syndrome in up to 20 percent of cases. In subjects who have this mild illness due to cytomegalovirus there is an acute T-cell dysfunction as severe as in our gay patients with *Pneumocystis carinii* pneumonia.[15-18] In addition, there is some experimental animal evidence that the severity of the immunosuppression is directly related to the size of the virus inoculum.[19] After some months, patients with previous cytomegalovirus mononucleosis have a return toward normal of their immune function. In the context of our gay patients there are at least two possibilities in terms of cytomegalovirus-induced immunosuppression. First, there may be a new particularly virulent strain of the virus being spread among a few homosexual men. Second, gay men may be experiencing so much repeated contact with semen containing this virus that they are having serial acute cytomegalovirus-induced immunosuppressive infections from which they remain permanently immunoincompetent.

Kaposi's sarcoma is a part of this epidemic, and there is a clear relationship between this tumor and cytomegalovirus. By electron microscopy, the virus has been found in Kaposi's sarcoma specimens.[20] In addition, portions of the virus genome have been identified in the genetic material of Kaposi's sarcoma.[21] Kaposi's sarcoma is felt to be a tumor that occurs in the setting of immunosuppression such as among renal transplant patients.[22] Cytomegalovirus, by causing a state of immunosuppression, could be causally related to the development of Kaposi's sarcoma. In my view, just as *Pneumocystis carinii* pneumonia is an opportunistic infection, I think it is clear that Kaposi's sarcoma is an opportunistic tumor. Perhaps both tumor and infection result from cytomegalovirus infection.

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Important Advances in Clinical Medicine

Epitomes of Progress — Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Injection of Steroid Agents in Solitary Bone Cysts

THE CAUSE OF SOLITARY (simple, juvenile, unicameral, benign) bone cysts is unknown, but most occur in the proximal ends of long bones in a growing skeleton. They are seen more commonly in male patients (2:1) and more than two thirds occur in the humerus and femur. They are ordinarily seen with a fracture through the thin cyst wall, but occasionally are noted as an incidental finding. An undisturbed cyst is filled with clear yellow fluid that has many characteristics of serum transudate. The cavity is lined with a membrane but has been shown to communicate directly with major regional veins.

Any pathologic fracture should be a cause for concern. Although carefully interpreted x-ray studies are pathognomonic in only 10 percent of cases, they usually establish a tentative diagnosis for reasonable early treatment. Immediate intervention risks the conversion of a closed fracture to an open one, but a properly managed fracture routinely heals without complication. Unless the cyst is obliterated, refracture can be expected. A few cysts (15 percent) will heal after one or more fractures, but if healing of a fracture does not proceed normally, a diagnosis should be made without delay. Diagnosis is confirmed by aspirating an amount of fluid compatible with the size of the cyst. If no fluid is obtained, it can be assumed that a solid tumor is present and biopsy is indicated.

Surgical intervention is the only effective treatment. A curettage and bone graft procedure is successful in a little more than half of cases. Extensive surgical treatment is probably more successful but is not advised in a routine case. Injection of cortisone in a solitary bone cyst was first reported in 1974, and subsequent observation and experience have shown an improved healing rate compared with curettage and grafting. Injection of cortisone requires general anesthesia and x-ray monitoring or image intensification, but is simple, requires minimal time in hospital, and results in minimal morbidity. Although multiple injections may be required in older patients or larger cysts, almost all will eventually respond. It is important to maintain surveillance of a lesion after apparent healing because recurrence is possible in a small percentage of cases. If the cyst has not recurred at the time of skeletal maturity, later occurrence is unlikely. It appears from the reported experience that injecting cortisone in a

unicameral bone cyst is a definite advance in the management of this perplexing and aggravating lesion.

TILLMAN M. MOORE, MD

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Methacrylate Cementation for Giant Cell Tumor

GIANT CELL TUMORS of bone are uncommon, composing approximately 5 percent of true neoplasms of bone. Most are benign but have the potential for metastasis in 2 percent to 6 percent of cases, primarily to the lung. Some studies report a slight female preponderance, and it is generally believed that the tumors occur in the epiphyseal region of the bone after the growth plate closes. About 50 percent occur around the knee but these tumors may occur in any part of the skeleton. They are most often seen in young adults, but may present at any age.

Histologically the giant cell tumor is almost indistinguishable from the brown tumor of hyperparathyroidism, so it is important that serum calcium, phosphate, alkaline phosphatase and perhaps parathormone levels be determined before a treatment plan is formulated.

Surgical intervention is the primary treatment of benign giant cell tumor of bone unless the location precludes reasonable surgical access. X-ray therapy is effective, but may be contraindicated except in extenuating circumstances. Curettage and bone graft failed to eradicate the tumor in almost half of reported cases; amputation is unnecessary in uncomplicated cases. An adequate en bloc resection results in the best local control, but often requires extensive and complicated reconstruction. For these reasons, implantation of methyl methacrylate resin after thorough curettage (wide marginal resection) is more frequently being done. The monomer is inherently toxic to the surrounding tissue, and the polymerization is exothermic, producing a surface temperature that approximates that of pasteurization. Because tumor cells in general are known to be heat sensitive and may be injured by the monomer, implantation of a large bolus of bone cement is theoretically beneficial in tumor control. There are two actual advantages, however. The joint and involved body segments can be rapidly rehabilitated following cementation. Also, gross persistence of tumor surrounding the radiopaque cement is easier to perceive on x-ray films, so that further treatment can be instituted without delay. If there is no evidence of tumor recurrence noted on follow-up evaluation, the cement can either be left in situ indefinitely or removed electively and the cavity filled with bone graft.

In at least one center, methacrylate implantation is done after cavitary cryotherapy using liquid nitrogen, usually followed by later bone grafting. In older or inactive patients who are candidates for total joint replacement, the involved bone can be resected, autoclaved—causing necrosis of the tumor—and returned immediately to the patient with methyl methacrylate supplementation. In this procedure, methacrylate is used to fill the space previously occupied by the tumor and to provide rigid fixation for the total joint implant.

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Limb Replantation

IN THE PAST TEN YEARS limb replantation has progressed from an experimental procedure done in only a few centers to a procedure that is available in many communities. The indications for replantation are now more clearly defined, as the techniques' surgical limitations have been tested and patients who have undergone such procedures have been observed for several years.

Avulsed, crushed and severely mutilated limbs are difficult if not impossible to replant because of widespread tissue destruction. Even the most cleanly amputated part is never normal following replantation. A shortened skeleton, stiff joints, diminished sensibility and cold intolerance are the commonly encountered sequelae, so a patient's functional interests are sometimes better served by having the amputation site closed rather than being burdened with a viable but dysfunctional part. The following sharp, relatively well-localized amputations are potentially suitable for replantation: isolated thumb amputations at any level proximal to the interphalangeal joint; multiple finger amputations at levels proximal to the distal joints, and hand, wrist and forearm amputations.

More proximal upper limb replantations may occasionally be done in younger patients. Lower limb replantations are rarely indicated because a prosthesis can substitute for the amputated part in a more functional, timely and economical manner.

When an amputation has occurred, bleeding in the proximal stump should be controlled by direct compression and elevation. The amputated part should be wrapped in a clean or sterile bandage and placed in a waterproof container such as a plastic bag or cup. The container should be placed on ice to keep the part cold but not frozen. Once cooled the amputated part can withstand at least several hours of anoxia, but the replantation procedure should be initiated at once. The primary physician should examine the proximal limb and the amputated part both visually and radiographically. With this information the physician can then contact a replantation center for consideration of patient transfer.

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Foot Problems in Diabetes Mellitus

RECENT ADVANCES in the treatment of diabetic foot problems have enabled physicians to significantly increase the percentage of feet and legs salvaged. Advances in the techniques of vascular assessment, revascularization and in limited amputation have enabled the salvage of many ischemic feet and legs. Use of the total contact cast with associated techniques has enabled salvage of legs that have neurotrophic foot ulcers.

Although clinical examination is still the principal means of vascular evaluation, use of the Doppler ultrasound stethoscope has enabled physicians to recognize pulsatile flow in an extremity, which cannot be detected by the usual clinical methods. With the use of the Doppler instrument and various-sized blood pressure cuffs, segmental blood pressures can be determined in a limb. A systolic pressure of 70 mm of mercury or higher or a pressure of at least 45 percent that of arm pressure is an indication that a limited amputation at that level can succeed or that an ischemic ulcer at that level can heal. Promising new techniques have been developed that can directly measure the vascularity and healing potential of skin. These include measurement of transcutaneous partial oxygen pressure (Po_2) and measurement of skin blood pressure and skin blood flow, both recently reviewed by Burgess and Matsen. The techniques of Doppler examination and limited amputation have been reviewed recently by Wagner. Toe amputations, transmetatarsal amputations, ray resections and Syme's amputations have been successful when leg to arm pressures are 45 percent or better by Doppler examination. A value less than 45 percent can, in some instances, be raised by an endarterectomy or a bypass graft and a limited amputation can then be done.

The total contact cast completely encloses a foot and leg in a clean, protective environment. It allows ambulatory treatment of foot ulcers when vascularity is adequate and when infection is under control. Adequate vascularity is determined by Doppler examination. Before application of the cast, the foot ulcer must be thoroughly debrided and a povidone-iodine dressing applied. Infections are treated by standard means and healing in the cast generally will occur in four to six weeks. A recurrence of the ulcer can be expected if the underlying pressure points are not relieved. This is done by wearing an extradepth shoe with a foamed polyethylene (Plastazote) insole or by surgical excision of bony prominences.

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The Treatment of Acetabular Fractures

THE CONCEPT has been held for many years that most displaced acetabular fractures are best treated with attempts at reduction and subsequent immobilization for many weeks by skeletal traction. The particular problems associated with this approach have been the less-than-adequate reduction of the articular surface of the hip, the frequent displacement of the head on releasing traction in central fracture dislocations and the early onset of degenerative changes in the joint. More recently the possibilities and advantages of open reduction and internal fixation of acetabular fractures have been advanced to parallel the accepted approach to other intra-articular fractures.

To arrive at a complete diagnosis and appropriate treatment plan for an acetabular fracture,

one must fully discern the fracture configuration in the anterior and posterior lips or columns of the acetabulum. Thus a radiologic examination, including Judet 45 degree iliac and 45 degree obturator oblique views, often supplemented by computerized tomography, is necessary. The appropriate incisions and order of approaches (anterior, posterior or lateral transtrochanteric) may then be planned and reduction and fixation with modern instrumentation and implants can be satisfactorily achieved. A reconstructive surgical repair of an acetabular fracture is not necessarily an emergency procedure; in fact, it is usually advantageous to obtain all the special radiologic studies and analyze them at leisure. An operation should, however, be done within three weeks of the accident, after which time bone union is advancing and reduction becomes very difficult.

Advantages of operative intervention in the treatment of acetabular fractures include being able to remove loose intra-articular fragments, obtain an anatomic reduction and stable internal fixation, facilitate early joint motion, dispense with traction and prolonged bed rest, permit early discharge from hospital, decrease the incidence of degenerative hip disease and facilitate future reconstructive operations if the latter supervene. Disadvantages of the surgical approach to treatment include the possibilities of infection and sciatic nerve injury. An acetabular fracture reconstruction can be lengthy and difficult and should be done by an orthopedic surgeon trained and experienced in such procedures.

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Rattlesnake Bites: Current Hospital Therapy

THE TREATMENT of persons bitten by rattlesnakes varies throughout the country. Some authors advocate that all envenomated patients undergo extensive surgical debridement and subfascial exploration. Others believe that even routine surgical procedures are too radical and suggest that antivenin given intravenously is the method of choice. This controversy has raged for many years.

Using a Wick catheter to measure interstitial fluid pressures in subcutaneous and intracompartmental tissues, we developed a laboratory model to better evaluate the effects of venom, antivenin and operative procedures on tissue pressure and destruction. A solution of 3 mg of desiccated crotalid *(Crotalus veridi helleri)* venom that was dissolved in 0.2 ml of normal saline was injected into the anterolateral compartments or subcutaneous space of canine rear legs. The pressure in these tissues was then monitored with Wick catheters and at 48 hours or longer, the dogs were killed and their compartments and tissues were evaluated histologically. From this study, we determined that only with direct intramuscular injection of the venom was there any involvement of the intracompartmental space. A fasciectomy done before the envenomation could help relieve the pressure, but had no effect on muscle destruction, as noted histologically. Conversely, high doses of antivenin modestly reduced the pressure rise, but definitely helped preserve the microscopic viability of the muscle cells.

Because of these studies we began a clinical project wherein all patients bitten by rattlesnakes had Wick catheter pressure determinations before treatment. If the intracompartmental pressures were less than 30 mm of mercury, no operation was recommended. In more than 15 patients evaluated, no surgical procedure was recommended, but high-dose antivenin was given intravenously and all patients responded functionally and systemically. All were in normal condition after three to four days.

Because of the basic science study, correlated with our clinical trial, we now feel there is sound rationale for avoiding surgical intervention and initiating a medical (antivenin) regimen in most patients following rattlesnake envenomation. If clinical evidence of envenomation develops, we initiate antivenin therapy and measure intracompartmental tissue pressure. If pressures measure over 30 to 40 mm of mercury, we recommend fasciotomy to reduce any additional insult to the compartment contents by the elevated pressure—an effect separate from that of the venom. In all cases, envenomated patients should receive antivenin of four to five vials per hour for adults and up to eight to ten vials per hour for small children. If a bite is subcutaneous and muscular involvement is minimal, we feel surgical decompression is unwarranted. To date we have cared for more than 700 persons envenomated by rattlesnakes,

with only one requiring surgical decompression. No neurologic or functional deficits have developed with this treatment regimen.

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Spinal Stenosis

THE ORIGIN OF SPINAL STENOSIS can be developmental, degenerative or a combination of both. In developmental stenosis there is a decreased interpedicular distance and a shortening of the pedicles, reducing the anteroposterior diameter of the canal. In the degenerative type, patients have canals of normal dimensions that become stenotic due to hypertrophic facets and lamina, posterolateral vertebral body osteophytes, disc herniation, ligament hypertrophy or spondylolisthesis. The stenosis can be in the central canal, the lateral recesses or at the intervertebral foramina.

Men are more commonly affected than women and the age of onset is usually in the fourth or fifth decade; however, it is seen in patients of all ages. Patients usually have both back and leg pains. About 40 percent will have pain in both legs that may be radicular. More often the leg pains are characterized by intermittent claudication, with patients describing a pain or heaviness in their legs, with or without muscle weakness, after walking a short distance. With a short period of rest the leg symptoms resolve, only to return again after an equally short distance of walking. These leg problems can be differentiated from a vascular origin by Doppler examination, electromyographic studies, bicycle exercise testing and arteriography.

On physical examination most patients are found to have absent reflexes and sensory and motor defects, but relatively few (less than 25 percent) have a positive result on straight-leg raising or Laséque's test. With stenosis, if these test findings are positive, they will usually be positive bilaterally.

Narrowing of the canal and hypertrophy or subluxation (or both), which strongly suggest the diagnosis, can be seen on plain roentgenograms. The newer generation of computerized tomography scanners with their improved resolution have been very helpful in the more difficult cases. Myelography studies will show posterior or lateral defects or an hourglass deformity at one or more levels and may show narrowing of the dural sac.

The only effective therapy is surgical decompression. It is important to be aware that in many cases the nerve compression is lateral under the hypertrophied facets. The laminectomy must extend laterally to decompress the nerve roots as far as the intervertebral foramina. This is accomplished by an undercutting partial facetectomy at all levels where preoperative studies have shown compression to be present.

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Vascularized Bone Grafts

VASCULARIZED GRAFTS of living bone offer an advantage over conventional nonvascularized grafts in that more osteocytes will survive and thus more rapid healing of bone will occur. Bone can be transferred as part of a composite tissue flap, along with skin and fat, and nourished by an attached vascular pedicle. The most common flap used in this manner is the groin flap, with a portion of the iliac crest nourished by the superficial or deep circumflex iliac artery and veins. Only relatively small defects can be covered by this type of flap and it cannot be transferred to the leg in a single stage except as a free flap.

Free vascularized bone grafts for defects in long bones caused by tumor or trauma have been possible with the development of microvascular surgical techniques. A recent review of the role of vascularized grafts in bone grafting has shown that for defects less than 6 cm conventional autogenous bone grafting techniques will generally work satisfactorily. For defects larger than 6 cm vascularized grafts are more satisfactory than conventional techniques.

The most suitable donor bone for long bone defects is the fibula. This bone is transferred on a vascularized pedicle of the peroneal artery and accompanying venae comitantes. Attached peroneus brevis muscle and overlying skin can also be transferred with this flap if needed as a functional motor and if the nerve supply to the

muscle can be reattached to a motor nerve at the recipient site.

Weiland and associates have recently reported on the cases of ten patients who underwent en bloc resection of a tumor or benign lesion and immediate reconstruction of the defect with free vascularized fibular grafts. Lesions resected included low grade chondrosarcoma, giant cell tumor, adamantinoma, fibrosarcoma and congenital pseudarthrosis of the tibia. Although the leg must be protected from weight bearing early on, all patients were fully weight bearing by 4 to 12 months postoperatively. Grafts were found to hypertrophy and only one failure was noted.

With the possibility of free vascularized bone grafts, the treatment horizons of preserving functional limbs can be expanded with low grade malignant and locally aggressive tumors. One can do adequate en bloc resection of a tumor without fear of creating a bone defect too large for reconstruction.

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The Role of Hyperbaric Oxygen in Orthopedics

HYPERBARIC OXYGEN (HBO) increases tissue oxygenation by a factor of ten or more. It is administered by placing a patient in a monoplace (one-man) or multiplace chamber and pressurizing the vessel to two to three atmospheres absolute (1,520 to 2,280 mm of mercury). The monoplace chamber is pressurized with oxygen and a patient breathes the oxygen in the chamber directly. The multiplace chamber is pressurized with air and pure oxygen is breathed by a patient through a mask. At three atmospheres pressure (2,280 mm of mercury) enough oxygen becomes dissolved in plasma to meet tissue needs in the absence of hemoglobin-borne oxygen. HBO supplements the oxygenation of ischemic tissues caused by low flow states, edema or anemia.

Gas gangrene, chronic refractory osteomyelitis and crush injury are the three orthopedic conditions for which HBO is most frequently given. However, it has been used in 31 other orthopedically related problems.

In the past HBO was used empirically, but today information exists for its rational application. For example, in gas gangrene it was thought that HBO's primary role was to kill clostridial organisms. Actually HBO first halts formation of deadly α-toxin and, second, it stops bacterial proliferation. The use of HBO in gas gangrene is adjunctive, as shown in the study of Demello and co-workers in which dog survival rates were improved 25 percent with HBO.

Misconceptions also existed in the use of HBO for the management of chronic refractory osteomyelitis. Instead of inhibiting growth of the offending organism, as originally thought, HBO helps to oxygenate the ischemic environment around the focus of infection sufficiently for leukocytes to kill microbes by oxidative mechanisms (Mader and associates).

In crush injuries and acute peripheral ischemias perfusion is often so compromised that repair processes ordinarily cannot occur (Strauss). Specific tissue oxygen tensions are required for neovascularization and fibroblast proliferation. HBO helps achieve these baseline tensions. This is also the proposed mechanism for HBO's usefulness in related conditions such as replantation operations, frostbite and compromised skin grafts.

There are two promising new uses of HBO in orthopedics. The first is in patients whose circulation is compromised, such as those who have diabetes or arteriosclerosis and those who have radiation vasculitis with infected, nonhealing wounds. Limb salvage is considerably improved when HBO is added to a comprehensive wound management regimen. Also, HBO substantially reduces muscle necrosis and edema in dogs that have experimentally induced intramuscular compartment syndromes.

Hyperbaric oxygen is remarkably free of untoward side effects. Complications such as oxygen toxicity, middle ear barotrauma and confinement anxiety are well controlled with appropriate preexposure orientations, medications and treatment schedules. Contraindications to HBO are few. Fever, acidosis and dehydration lower the threshold for oxygen toxicity and should be corrected before treatments are started. Nicotine use makes HBO ineffective and should be discontinued during the course of treatments. Viremias may become fulminating infections during HBO exposure and thus are an absolute contraindication to its use. Pregnancy is a relative contraindication because of possible teratogenic effects.

Orthopedic indications for HBO will become

better defined with perfection of the techniques for direct measurement of tissue oxygen tensions and intramuscular compartment pressures. Its use then will be based on objective measurements rather than diagnoses. Probably HBO's most promising orthopedic role will be as an adjunct to the management of wound healing and trauma.

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Surgical Management of Scoliosis

WITH THE ADVENT and support of school-based screening programs, there appears to be a definite decrease in the number of cases of more severe idiopathic scoliosis being seen on initial evaluation. The cost effectiveness of such screening has been well established. A certain number of patients continue to be seen, however, who have undetected large-curve idiopathic scoliosis. Some patients will not cooperate in preventive programs of bracing and progression of their curvatures may occur.

In the past 20 years, instrumentation for the surgical treatment of scoliosis has been developed and refined. The surgical spinal instrumentation procedure is routinely augmented by a spinal fusion using harvested autogenous bone, usually from the iliac crest. When autogenous sources are deficient or inadequate in amount, homologous bank bone can be used solely or to augment inadequate amounts of autogenous bone. Surgical intervention is generally reserved for thoracic curvatures of more than 40 degrees, particularly in skeletally immature persons with decompensated spinal alignment. Similarly, lumbar curvatures of more than 50 degrees are usually managed surgically. In addition, adults in whom pain has developed or in whom evidence of the progressive curve increase is recorded (or both) may also be candidates for surgical correction and stabilization.

The Harrington rod instrumentation and spinal fusion procedure is the standard technique used in most cases. The surgical approach is directly posterior, in which the paraspinous muscles are separated subperiosteally from the lamina out to the transverse processes. After instrumentation and correction the spinal fusion is done by laying bone graft on the decorticated bone surfaces thus exposed. Large spinal curvatures in patients with neuromuscular handicaps and curvatures greater than 70 degrees and involving lumbar and thoracolumbar areas with exaggerated lumbar lordosis are often best treated by a combined anterior and posterior approach. Initially an anterior thoracicoabdominal retroperitoneal approach to the spine is made and the intervertebral discs are removed. The anterior spine can be supported with various devices that include a Dwyer or Zeike apparatus; this enables excellent correction and stability. In about two weeks a second step is done by a posterior Harrington rod and spinal fusion procedure, which provides additional correction and improves stability and chances for successful fusion.

Recently segmental posterior spinal instrumentation has been developed and seems well suited to patients who have neuromuscular complications and who poorly tolerate postoperative casting support or braces. In this posterior fusion technique, longitudinal rod devices are also used. Wires are looped around the lamina at each level or segment and are secured to the longitudinal rods by twisting tightly. This provides a very stable fixation and is combined with a bone grafting fusion technique. Although surgical corrections afforded by this technique are similar to the Harrington rod procedure, the improved stability of the device obviates the need for postoperative cast or brace support, which may prove to be an advantage. The increased potential for technical problems with the segmental procedure and longer operating time may be drawbacks, however.

Intraoperative or procedure-related complications have also been subject to new developments. The potential problem of blood transfusion required during most procedures has been altered by autogenous donor programs for older adolescents and cell-retrieval systems that allow shed erythrocytes to be collected and recirculated. The ever-present potential for paralytic complications occurring during surgical procedures of the spine can now be assessed by spinal cord monitoring techniques in which evoked potentials are recorded during the critical elongation or stretching stage of the procedure. Although at this time we do not fully understand the meaning of these evoked potentials, these techniques have been shown to be sensitive enough to recognize cord

conduction problems. This seems to be a better controlled and safer monitor than the prior practice of waking the patient during the operation to assess voluntary motor function in the legs.

Surgical treatment for scoliosis is a relatively safe procedure. When these techniques are applied to a patient who has the proper indications, in an environment with appropriate controls and experienced management, they can prevent disabling deformities, afford correction of established curves and prevent disability resulting from uncontrolled curve progression.

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Orthopedic Management of Patients With Multiple Injuries

DURING THE PAST FEW YEARS, experience from trauma centers suggests that immediate stabilization of fractures effectively decreases morbidity and mortality of patients with multiple injuries.

Meek and co-workers compared victims of multiple trauma whose long bone fractures were fixed in the first 24 hours after injury with a similar group treated more traditionally. The mortality of the early fixation group was 1 in 22, that of the control group was 14 in 49.

Secure stabilization of skeletal injuries gives patients more mobility and reduces the need for narcotic analgesia, thereby improving pulmonary care. Moreover, the incidence of posttraumatic respiratory distress syndromes is decreased. Continuing blood loss into fracture sites may also be reduced by rigid fixation. Nursing care is simplified, compared with that required for patients in skeletal traction and cumbersome plaster casts.

In addition to systemic benefits, successful application of demanding techniques of wound care and fracture immobilization appears to lower the risk of fracture infection, nonunion and malunion. It also permits earlier rehabilitation of the injured parts, with less likelihood of permanent functional impairment.

It is crucial to plan the management of skeletal injuries in the context of the whole person. A well-organized trauma team is basic. Immediate fracture fixation should be undertaken only if it will not interfere with more urgent life-saving needs, if it will provide sufficient stability for early patient mobilization and if it will enhance the total care of patients.

Expertise and equipment should be available for screw and plate fixation, intramedullary nailing, external skeletal fixation, Harrington rod spine fusion and functional bracing techniques like the halo-jacket and roller-traction cast-brace. Multiple surgical teams are desirable, to expedite the operative procedures.

Total care of multiply injured patients must include complete, prompt diagnosis of all injuries, with urgent treatment of cardiorespiratory, cerebral and abdominal problems that threaten survival. Unstable spine injuries must be managed so that the spinal cord is protected. Sepsis must be prevented. Effective care of other injuries will minimize their complications and maximize functional recovery. Patients' nutritional needs must be anticipated and met.

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Arthroscopic Surgical Techniques

ONE OF THE most exciting developments in orthopedic surgery during the past few years has been arthroscopy and arthroscopic surgical techniques. As Casscells has pointed out, arthroscopy has been accepted as the most accurate diagnostic test for knee joint problems. In many areas of North America, arthroscopy represents the most common orthopedic procedure done.

The arthroscopic operation is a logical extension of diagnostic arthroscopy, the concept being: if you can see the lesion with the arthroscope, then fix it with the arthroscope. Essentially the technique involves the use of miniature cutting, biting and grasping instruments to carry out standard surgical repair of the knee through small puncture wounds. In the mid 1970's, arthroscopes with improved optics became available and miniaturized instruments were perfected, enabling surgeons to begin developing arthroscopic surgical techniques. In the late 1970's motorized instruments became commercially available and the arthroscopic revolution was under way.

Patient enthusiasm has been a major impetus for the rapid development of arthroscopic oper-

ative techniques. The major advantages are decreased morbidity, rapid recovery of function and small scars. An arthroscopic meniscectomy in a healthy patient requires only a short hospital stay or an outpatient visit, and often the patient can return to normal activities within two to three weeks. The published rates of complications are much lower than with open arthrotomies for the same procedure.

The range of procedures that are being done arthroscopically has expanded dramatically. Initially the operations were limited to the removal of loose bodies, obtaining synovial biopsies, treatment of patellar malalignment and resection of meniscal tears. Techniques are now being perfected for the treatment of osteochondritis dissecans, degenerative arthritis and postsurgical fibrosis. Experimentally, development is proceeding with techniques for the suture of torn menisci, the reconstruction of anterior cruciate ligaments and the use of lasers for surgical repair of joints.

It is too early to assess the long-term results of arthroscopic operative techniques, but, as noted above, the short-term results have been excellent. The intermediate-term evaluation of arthroscopic meniscectomies indicates that the results are comparable with or better than those obtained with standard techniques two to five years after an operation.

There are two major disadvantages of arthroscopic operations. First, the technique is difficult to learn and to do. Most skilled arthroscopists feel that it requires the experience of about 100 diagnostic procedures to reach a satisfactory level of proficiency to begin surgical work. They also agree that most surgeons will require 50 to 100 arthroscopic surgical procedures to become comfortable with the technique. Second, delicate and expensive equipment is required for arthroscopic operations, and this equipment will not be available at every hospital. The short-term effect of these two factors will be to limit the number of orthopedic surgeons who do arthroscopic operations.

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EDITORIALS

Is It Time for a Fundamental Reexamination of Medical Education?

THE AMERICAN MEDICAL ASSOCIATION has completed and its House of Delegates has adopted a report by the Council on Medical Education entitled "Future Directions for Medical Education." The report has 36 recommendations which address many facets of medical education including specialty training, continuing medical education, practice performance and the training of foreign medical graduates, as well as preparation for medical school and the curricula in medical schools. The Association of American Medical Colleges has just embarked on a three-year study of "the general professional education of the physician—the eight years that include college preparation and medical school." And the Institute of Medicine of the National Academy of Sciences has begun a one-year project to prepare a plan for a major review of medical education in the United States. There is a real need for a reexamination of medical education at this time and these three generic organizations are to be commended for their interest and willingness to have a go at it.

In 1910 a study commissioned by the American Medical Association (to become known as the Flexner Report) firmly rooted medical education in the then nascent biomedical science. This orientation became institutionalized and has persisted. As the amount of biomedical knowledge increased in subsequent decades it became impossible to teach or learn it all in the four-year medical school curriculum, or for any one physician to practice competently throughout the whole gamut of medicine, for that matter. Specialities and specialty training began to appear and this has now become the order of the day, with the result that additional years of training (three to seven) have been added beyond the four years of medical school, and a complex system of specialty boards and specialty training is now in place. Medical knowledge continues to increase (some say it doubles every five to ten years) and the time seems to be coming when further add-ons of years in the formal preparation for practice will become impractical, if indeed this is not already so. Perhaps, as was the case in 1910, there is need once again for a fundamental reexamination of medical education.

It seems that the inexorable and certainly welcome progress in biomedical science has had at least three important effects on medical practice and patient care that have yet to be fully taken into account in medical education. First, there is the sheer mass of medical knowledge now and what may be expected in the future. It has long since been obvious that no medical student or physician can any longer hope to learn or remember all that he or she should know, and furthermore it has become obvious that what needs to be known and used in practice is changing all the time. Especially to deal with the changing nature of medical knowledge, medical education should be viewed and structured more as a continuing process than is the case at present. Second, the specialization in medical education and medical practice that has occurred as a result of the proliferation of reductionist biomedical science has been at the expense of less attention being paid to two factors: (1) the oneness of this science (the interdependencies among the specialties or subspecialties) and (2) the wholeness of the person

whose illnesses or health and well-being are often, if not always, the resultant of complex interactions among the body systems (and this includes the mind) and with the external physical and social environment of the person. It has become all too evident that reductionist medical science alone does not teach all that is needed for good patient care. And third, the development of biomedical science and the implementation of new technology in patient care has had not only human, but social, economic and political ramifications, which now have come to impinge directly and significantly on every physician's practice, in whatever specialty, and upon the health, illness and well-being of patients.

It would seem that the time may have come for medical education to become more efficient in dealing with expanding and changing medical science and to expand its horizons in what amounts to a new era of medical practice and patient care. If it is true that no one can remember or keep up with all of the medical knowledge (especially if its scope is now to include a better understanding of human nature and human behavior and all of the social, economic and political ramifications of medical science as these affect a physician's practice and patient care) then medical education may need to provide a medical student or practicing physician with some kind of a conceptual framework for an awareness of the whole gamut of medical knowledge, and then the skills and tools to retrieve needed specific information, elsewhere than from memory, when and where it is needed. It would be important to teach and learn the skills of what is being called self-directed learning throughout the whole continuum of medical education. If it is true that illness, health and well-being are the resultant of complex interactions among and between the internal and external environments of the mind and the body, then the scope of medical knowledge should be expanded to include an awareness of the capabilities and limitations of all the specialties of medicine that deal largely with the systems of the internal environment and also an understanding of the interaction of persons, both sick and well, with their physical and social environments. And if it is true that social, economic and political forces now impinge significantly on medical practice and patient care, then these too should be taken into account in medical education now and for the foreseeable future.

To accomplish what has been suggested will clearly require some new and quite different approaches in medical education. Changing science and the reality of the oneness of all medical knowledge will surely require that medical education be viewed as a true continuum from the moment of decision to enter medical school through a lifetime of practice. A framework or skeleton of the totality of medical knowledge may need to be constructed and means developed for a self-directed physician or student learner to retrieve up-to-date information when and as needed, and at whatever level of training or practice. And it may be that medical education throughout the continuum should be more patient centered, more problem centered and more learner centered than it now is.

For these as well as other reasons it would seem that a major new approach to medical education is what may be needed rather than some further fine tuning of the present way of doing things.

—MSMW

Fasting

Dr. Kerndt and co-workers present in this issue an extensive review of the metabolic and clinical changes associated with fasting. Only a single case report forms the nidus of this review, but many of the more important changes of fasting can be seen in this one patient.

During evolution humans have developed exquisite and highly efficient means for dealing with food deprivation.[1] The same, unfortunately, is not true for prolonged periods of caloric excess. This is not surprising. Starvation must have been a formidable evolutionary force in that survival strongly favored those who had an efficient means of storing fuel, mechanisms for using alternative sources of fuel and methods of modulating fuel usage. All of these topics are considered by Dr. Kerndt and colleagues. In attempting to comment on the most clinically relevant parts of this review only a few points can be emphasized. I might add, however, that the role of fasting in accelerating weight loss in obesity is a topic that usually intrigues obese persons—and hence presents a problem to clinicians.

Humans, even when nonobese, have adequate fat stores to meet all caloric needs for two to three months. This is not the problem of a total fast. The critical danger of a prolonged total fast

is that protein in the body constitutes only 15 percent of total energy stores, and depletion of a half to a third of these stores is incompatible with life. Because we have neither an exact means of predicting this point during a fast, nor of determining individual vulnerability to protein loss during prolonged periods of fasting, starvation (in excess of several days) to reduce weight should probably be avoided.

A second point of importance that militates against using prolonged fasting for weight loss is the simple fact that it becomes a less effective means of weight loss the longer the fast is maintained. This is nicely shown in the single patient studied by Kerndt and associates. The rate of weight loss in the patient was 0.9 kg per day during the first five days of fasting. By the third week it was 0.3 kg per day, and one can safely predict that it would be even less by the fourth or fifth week. Two important adjustments occur during fasting that change the rate at which body weight is reduced: First, serum triiodothyronine (T_3) concentrations decrease during fasting such that they reach levels recorded in the hypothyroid state.[2,3] Associated with the decrease of T_3 is a concomitant lowering of the basal metabolic rate. The latter phenomenon was actually recognized by investigators many years before the development of means of measuring T_3. The change in the T_3 level is an important adaptive mechanism that assures that the body burns only that fuel which is necessary for the most essential functions. In essence, the thermostat is turned down.

Second, ketosis itself, a phenomenon considered in detail in this study, induces changes in ketone excretion. Ketosis results in a reduced capacity of the kidney to excrete ketones, which in turn permits a decrease in the mobilization of free fatty acids.[4] In essence, ketones remain available over a longer period of time for fuel usage. These two changes limit body weight loss during the later phases of a fast from a third to a fourth of that achieved during the initial phase of fasting.

The findings on multiple diagnostic tests can be altered by fasting, and this general fact requires emphasis. Changes in the serum concentrations of hormones not directly related to balancing substrates are well documented. The levels of follicle-stimulating hormone and luteinizing hormone, for example, clearly decrease during fasting, along with changes in T_3, insulin and glucagon levels. A failure to appreciate this leads to ridiculous conclusions by the uninformed.

One is reminded of the situation in which an intern and a resident ordered thyroid function studies on the same patient. The resident ordered a T_4 and the intern ordered a T_3. When the results of the T_4 returned, they were compatible with mild hyperthyroidism. When the T_3 findings returned, the intern began treating the patient for hypothyroidism. In general, any condition in which starvation plays a prominent role can be expected to yield a plethora of abnormal laboratory values which, if considered in a simplistic fashion, lead to erroneous and often ludicrous conclusions.

The basic information summarized in this review can provide practitioners with multiple insights into clinical problems. Because the review is of necessity somewhat encyclopedic, it might, like fasting, be reconsidered in small sections.

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Acquired Immune Dysfunction in Homosexual Men

It is well established that a severe acquired immunodeficiency syndrome is occurring with increasing frequency among homosexual men.[1-3] The dramatic presentation of these cases leaves little doubt that this is a new syndrome and not a previously unrecognized disorder. Elsewhere in this issue Dr. Jeffrey Golden presents the clinical features of six homosexual men with *Pneumocystis carinii* infection. One of these patients died and the others are under follow-up evaluation. Clinical studies and long-term evaluation will be essential to determine whether there can be significant clinical and immunologic recovery from the acquired immunodeficiency found in these patients.

The cause of the acquired immunodeficiency in

homosexual men is not clear. Multiple factors have been implicated including drug use (marijuana, amyl nitrite and other agents), specific infectious agents such as hepatitis virus and cytomegalovirus, immunosuppressive effects of multiple simultaneous infectious agents and factors related to the homosexual life-style including oral-anal sexual contact and promiscuity.[4] It is unlikely that any single factor will emerge as the sole agent responsible for this severe acquired immunodeficiency.

What is most striking about the acquired immunodeficiency in homosexual men is its severity. Those persons in whom opportunistic infections develop have T-cell immunity that is less than 10 percent of normal. This degree of immunodeficiency usually occurs only in primary congenital immunodeficiency disorders. This degree of immunosuppression does not develop even in patients who receive radiation therapy or immunosuppressive therapy for malignancy. Immunologic abnormalities in acquired immunodeficiency in homosexual men include severely depressed T-cell numbers, a pronounced suppression of helper T cells associated with a concomitant increase in suppressor T cells and an abnormal response of lymphocytes to mitogens, allogenic cells and antigens.[1-3] Although immunoglobulin levels are normal to elevated, there is preliminary evidence that the severe T-cell impairment may also result in abnormal B-cell immunity.

Cytomegalovirus infection has received major attention as a possible infectious agent responsible for acquired immunodeficiency. The virus is strongly implicated as a cause of Kaposi's sarcoma in the homosexual population and virtually all homosexual men have evidence of continuing excretion of this virus. Repeated infection with cytomegalovirus alone, or in conjunction with other viruses, could result in rapid loss of T-cell function with susceptibility to opportunistic infection or malignancy.

Loss of immunologic function or immunologic attrition ordinarily occurs with aging. Thymic involution begins during teenage years and laboratory evidence of reduced T-cell immunity appears somewhere beyond 65 years of age.[5] In normal aging, the profile of immunologic attrition is similar to that found in acquired immunodeficiency in homosexual men, although the severity is not as great. It appears that the homosexual population is susceptible to an accelerated immunologic attrition that begins early in life and may be complete by age 35 to 45. Accumulating evidence suggests that the acquired immunodeficiency in the homosexual population is a result of repeated infection with the same or multiple viral agents. Even apparently healthy homosexual control populations have evidence of immunologic dysregulation as evidenced by reversed helper T-cell and suppressor T-cell ratios.[6,7] Transient reversal of helper-suppressor T-cell ratios occurs in nonhomosexual populations following viral infections, in particular hepatitis and cytomegalovirus.[8,9] However, in nonhomosexual populations, return of immunologic function occurs two to four weeks following acute viral infection. In the homosexual population it is possible that repeated viral infection, superimposed on an immunosuppressive state from a previous viral infection, could result in accelerated immunologic attrition.

As yet, there is no evidence to suggest that the acquired immunodeficiency found in homosexual men is reversible. Long-term follow-up studies of patients will be required to ascertain if clinical and laboratory improvement occurs spontaneously.

A number of approaches toward the treatment of patients with acquired immunodeficiency can be used. Patients with a known history of *Pneumocystis carinii* pneumonia or patients with documented severe immunodeficiency should receive trimethoprim-sulfamethoxazole therapy directed toward the prevention of *Pneumocystis carinii*. Patients with severe immunosuppression are probably also susceptible to fatal graft versus host reaction following transfusion of unirradiated blood products.[10] Therefore, all blood products administered to these patients should be irradiated to prevent this complication.[11] In addition, as blood products are known to transmit a variety of infectious agents, blood products should be selected from donors who are negative for antibodies to certain viruses such as hepatitis and cytomegalovirus.[12] If acquired immunodeficiency is related to multiple and repeated infections, then alteration of life-style with reduced frequency and types of exposures would be appropriate. Therapy with antiviral agents offers little promise because of the limited spectrum of antiviral activity as well as the emergence of resistant strains of virus. Active immunization directed toward specific viral agents such as hepatitis would be an important approach toward the prevention of infection. A new experimental cytomegalovirus

vaccine may become available in the future. Passive therapy directed toward the prevention of multiple infections should be evaluated. Gammaglobulin, in particular intravenous gammaglobulin, administered regularly has been associated with significant reduction in infection in primary immunodeficiency disorders.[13]

Immunotherapy, directed toward the reconstitution of T-cell immunity, offers potential in severely immunosuppressed patients. Aggressive therapy consisting of thymus transplantation or bone marrow transplantation has significant risk in patients with multiple infections. A number of thymic factors have been evaluated in primary immunodeficiency disorders and are being considered for patients with acquired immunodeficiency disease.[14] It is possible, however, that the degree of immunologic impairment has gone beyond that which can be reconstituted by thymic factor therapy.

Future studies should be directed toward ascertaining the specific causes of the acquired immunodeficiency, the potential spontaneous reversibility of the immunodeficiency and therapy capable of providing additional protection against immunologic attrition as well as reconstitution of immunity.

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How About Organizing 'Friends of Medicine'?

THE MEDICAL PROFESSION and organized medicine seem to find themselves in a paradoxical position with respect to public opinion and public support. Physicians and even organized medicine continue to rate very well in public opinion polls that purport to measure such things as trust, integrity and performance. Yet in their public image, as this is reflected in the informational media and in public rhetoric, they seem to be depicted too often as self-serving, noncaring, unduly rich and dedicated to personal and professional self-aggrandizement. From this it would seem that it is public image rather than public opinion that has brought about a progressive deterioration in the way the medical profession and organized medicine are viewed in the political arena. Somehow the favorable public opinion of trust, integrity and good performance has lost much of its political clout and the public image (which like all images is unreal) seems to be having a growing impact upon the economic and political fortunes of the profession. This is a matter of some concern since so many issues affecting health and patient care are now being decided in the political arena.

In our political system the votes are what decide the issues. Physicians are not and never will be a significant voting block. Political action committees (the PAC's) and the devoted support of medical society auxiliaries have greatly strengthened the profession's hand. But these do not bring the strength of those responsible for the favorable public opinion polls fully to bear either to influence the profession's public image or the fortunes of physicians and their patients in the crucibles of political decision. Some ways need to be found to strengthen the voter base of the medical profession and patient care. How is this to be done? There are many patients, former patients, and friends and families of patients who could rally around physicians and their medical societies to become more organized "Friends of Medicine" for community and political action in behalf of the medical profession and better patient care. Organized groups of such "friends" are nothing new, especially in the health care field, and they make possible an enormously expanded base of community and

public support through their voluntary efforts. They can and do significantly influence the votes of others.

The public opinion polls show that medicine has many uncounted friends. It seems reasonable to assume that many of them are waiting and willing to be called upon. With clear direction and clear and worthwhile purposes, organizations of "Friends of Medicine" could help carry many of medicine's torches for the betterment of the medical profession, patient care and the health and well-being of the public in local communities and in the legislative scene. And perhaps in turn the profession itself could get some helpful advice from these "Friends of Medicine."

—MSMW

Overdose With Tricyclic Antidepressants

THIS ISSUE CONTAINS a report by Michael Callaham discussing one of the most difficult problems facing a clinician dealing with acute overdose. Despite the seriousness and frequency of tricyclic antidepressant (TCA) overdose, little information is available to clinicians for making critical decisions concerning a patient's care. How serious is the overdose? Does the overdose warrant hospital admission and, if it does, how long should a patient be monitored and when can discharge safely occur?

Because there are few firm guidelines to follow, internists and the psychiatrists must work together to answer these questions. Most of the studies on tricyclic antidepressant overdose have been single case reports. However, recently Spiker and associates[1,2] reported two series of tricyclic antidepressant overdoses in which plasma levels and clinical findings were correlated. Bailey and colleagues[3] and Langou and co-workers[4] supplemented previous reports with two other series of patients with TCA overdose. These reports, as well as the study presented in this issue make it clear that there are few clinical symptoms or signs that are reliable indicators of the seriousness of the overdose or the probable clinical outcome.

Spiker and co-workers found that high plasma levels were always associated with cardiac arrest, grand mal seizure, tachycardia (heart rate higher than 120 beats per minute), cardiac arrhythmia and wide QRS (wider than 0.10 seconds) accompanied by or leading to unconsciousness or death. Furthermore, they found that the only strong indicator of high plasma TCA levels[3] (greater than 1,000 ng per ml) was a wide QRS (greater than 0.12 seconds) in the electrocardiogram and also that there was a weak correlation of overdose with pupil size estimated clinically. On the other hand, Bailey and associates[4] found that plasma levels of TCA did not correlate well with physical findings or most electrocardiographic changes. Nevertheless, in this report those patients with a QRS interval greater than 0.10 seconds had significantly elevated plasma levels. In addition, these authors found that a plasma level ratio of parent drug to metabolite greater than or equal to 2.0 was associated with acute overdose. Bailey and co-workers recommended that such a ratio be considered a meaningful indicator in the evaluation of acute overdose, because many patients in their study had blood levels in the therapeutic range and no major symptoms or signs of acute overdose. Acute overdose does not represent a steady state condition, so that tissue level may be higher than plasma level. Furthermore, this drug is highly concentrated by the myocardium.[5] Nevertheless, unlike other overdoses, plasma level of TCA represents a cornerstone of the management of patients. The most common physical findings in large series of acute TCA overdose were tachycardia and pupillary dilatation, which were noted in more than 40 percent of the cases. Hyperreflexia and hypotension, although noted in some patients, were less frequent.

The pharmacology of TCA has been studied extensively. These drugs have a number of pharmacological actions that include anticholinergic activity, direct myocardial depressant activity, and sympathomimetic activity, which is related to their ability to block the reuptake of amines. All of these actions may contribute to the adverse effect of TCA in acute overdose. However, the individual dose-response curve for each of these actions remains undefined. The cardiovascular effect of large doses of TCA's is an exaggeration of the effect of the drug at therapeutic levels and may be the identifying features of TCA overdose.

The literature contains a number of reported cases of delayed complications in which the physicians caring for the patients were unable to predict fatal outcome from the early clinical signs. Most of these complications were related to the cardio-

vascular system. It appears appropriate at this point to review the cardiovascular complications of TCA overdoses.

Arrhythmias

Arrhythmias have frequently been reported in the setting of tricyclic overdose. Sinus tachycardia may be directly attributed to the anticholinergic effect of this drug, or to a multiplicity of other factors, including hypoxia and acidosis. Yet, aside from sinus tachycardia, arrhythmia, as opposed to conduction abnormalities, is relatively uncommon. In the instances of massive overdose, arrhythmias may be the immediate cause of death.

Thorstrand[6] carefully evaluated 153 consecutive patients admitted, predominantly with tricyclic overdose, to an intensive care unit. The average TCA overdose was 1.048 mg. While the average initial heart rate was higher than when patients recovered, all but four were in sinus rhythm. These four had nodal or ventricular rhythms and were among the five patients who died. All of these patients had taken massive overdoses. Thorstrand concluded that 1.5 to 2.0 grams or more are necessary for development of arrhythmia in adults. Similarly, Vohra[7] and Bailey and colleagues[3] did not identify arrhythmia other than sinus tachycardia in their patients with tricyclic overdose. In one series of patients with TCA overdose, all of whom recovered, sinus tachycardia was present in 71 percent.[4] Initial drug levels in these patients were imipramine plus active metabolites 150-1,700 ng per ml; and amitriptyline plus active metabolites 180-1,560 ng per ml. While 6 percent had supraventricular tachycardia and 34 percent had severe ventricular ectopy, none of the patients had sustained repeated ventricular tachyarrhythmia in the hospital. Three of the patients with significant ventricular ectopy reportedly had a cardiorespiratory arrest prior to admission. Ventricular ectopy persisted after 72 hours but resolved within 36 hours in the majority of patients. Lidocaine hydrochloride was administered to these patients with no undesirable effects.

Conduction Disturbance

In contrast to arrhythmia, conduction abnormalities are observed frequently in cases of TCA overdose. In a study of 30 overdose patients, QRS duration was prolonged in 7, and significantly related to serum TCA levels.[3] In two series,[1,2] QRS duration also correlated with TCA levels, and in Thorstrand's examination of ten patients with TCA overdose,[6] all had QRS prolongation when first examined. Resolution of these electrocardiographic changes was associated with recovery. Vohra and associates[7] saw His bundles in the electrocardiograms of four patients with tricyclic overdose. Surface electrocardiograms of three of the patients showed QRS prolongation; all had normal HV interval on admission to hospital. Three patients with QRS prolongation had HV intervals of 70 to 90 ms, normal up to 60 ms, conduction from the AV node to the ventricle. All patients responded normally to the stress of atrial pacing with respect to HV prolongation. In addition, it was noted that the respective HV interval did not change. When electrocardiograms were done on these patients eight days later, at a time when all had recovered, surface electrocardiograms on conduction intervals were normal. Langou and associates[4] also found a high incidence of conduction abnormalities in patients with TCA overdose. PR prolongation was seen in 11 percent, QRS lengthening in 29 percent and prolonged QT intervals in 86 percent of the cases.

Thus, in toxic doses, tricyclics have an exaggerated effect, producing conduction abnormalities and, less commonly, arrhythmias by a mechanism similar to that of quinidine—that is, primarily by prolongation of the distal Purkinje conduction. The above mentioned changes are reversible and clearly different from those secondary to the anticholinergic effect of this drug.

Hypotension

The second most common cardiovascular manifestation of TCA overdose occurred in about 50 percent of the cases. Initial studies of patients with a suspected diagnosis of TCA overdose reported no change in supine blood pressure but a significant frequency of postural hypotension. These changes were observed especially in patients with organic cardiovascular disease. Subsequently, it was documented that postural hypotension was independent of age, sex, blood pressure or blood level of TCA. The mechanism whereby TCA produced hypotension is unclear, but it has been attributed variously to a peripheral effect, a myocardial depressant effect, a direct effect upon the central nervous system or a combination of these inferences.

In summary, tricyclic antidepressants have

many effects on the cardiovascular system, both directly and as mediated by the autonomic nervous system. They exert an effect similar, but not identical, to that of quinidine on the cardiac conduction system. Contrary to their reputation, TCA's may actually exert an antiarrhythmic effect at therapeutic levels. TCA's do prolong cardiac conduction, but this is generally not of clinical consequence, even in patients with underlying conduction system disease. Evidence that TCA's depress myocardial contractility in normal patients, even in the setting of large overdoses, is lacking. In contrast, orthostatic hypotension, possibly as a result of afterload reduction, may be a significant problem in patients with tricyclic overdose. This condition has been observed to be more common in elderly patients and in those with underlying cardiovascular disease.

Callaham, in his paper, recommends a very reasonable practical approach to the management of TCA overdose. In agreement with reports in the literature, he suggests that in the presence of persistent sinus tachycardia, wide QRS in the electrocardiogram, arrhythmias, dilatation of the pupils, or any kind of alteration in the level of consciousness, the patient should be observed for at least 48 hours with electrocardiographic monitoring. This suggestion is based on the finding in most of the series reported that most of the changes seen in patients suffering from overdoses with TCAs have appeared within 36 hours and could be treated successfully.

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CASE REPORTS

Refer to: Callaham M: Admission criteria for tricyclic antidepressant ingestion. West J Med 1982 Nov; 137:425-429

Admission Criteria for Tricyclic Antidepressant Ingestion

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COMPLEX AND SOMETIMES fatal complications make an overdose with a tricyclic antidepressant (TCA) one of the most difficult drug overdoses to manage. A further difficulty for a physician lies in assessing how much of the drug has been ingested by a patient who may appear clinically well. An illustrative case follows.

Report of a Case

A 38-year-old woman was brought to the emergency department at 9 PM stating she had taken a bolus of 20 to 30 of her mother's 50-mg desipramine tablets and an unknown quantity of alcohol two hours earlier. She had an empty bottle of the drug, and her mother confirmed the history. No other drugs were involved and the patient was not being treated with any other medications.

The patient was alert and oriented, and her speech was normal. Her blood pressure was 140/95 mm of mercury, the pulse rate was 125 per minute, respirations were 28 and temperature was not taken. On physical examination, the patient was noted to be obese; bowel sounds were present but hypoactive. The electrocardiogram (ECG) showed a sinus tachycardia with a rate of 125, normal axis, QRS duration of 0.10 seconds, QT interval of 0.35 to 0.38 seconds and PR interval of 0.18 seconds. Earlier ECG's were not available for comparison. The patient was given 30 ml of ipecac by mouth. Copious emesis resulted in the recovery of pill fragments. Charcoal and cathartics were not administered. Toxicologic studies done at this time showed a blood alcohol level of 0.04 percent, and a blood desipramine level of 0.02 μg per ml (therapeutic range 0.02 to 0.16 μg per ml). No traces of barbiturates, meprobamate, glutethimide, methyprylon, ethchlorvynol, chlordiazepoxide, diazepam or methaqualone were found. The laboratory uses a gas chromatography method with nitrogen-phosphorus detectors to test for TCA; the standard deviation of controls at 0.02 μg per ml is 0.0003 μg per ml. Blood gas and chemistry tests were not done.

The patient's clothing and belongings were removed and she was closely observed for the next six hours in the emergency department. Hourly ECG's remained the same as the first except for tachycardia, which gradually declined. Blood pressure stabilized at 120/90 mm of mercury. At 3 AM the patient was awake and alert, talking coherently and clearly, and was able to walk to the bathroom unassisted. Because she was constantly observed, and because all her personal belongings had been removed, it is exceedingly unlikely she ingested desipramine a second time in the emergency department. She was transferred to the psychiatric emergency department for evaluation; at this time her ECG was normal and pulse rate was 96 to 100 per minute. Upon entering psychiatric emergency at 3:30 AM her blood pressure was 120/90 mm of mercury, her pulse rate was 108 per minute, respirations 22 per minute and temperature 37.1°C (98.8°F). She was awake and alert but slightly unsteady on her feet. When seen by a psychiatrist at 5 AM her gait was unsteady, her speech was slurred and she was apparently having auditory hallucinations from time to time. She became increasingly agitated and fearful.

At 5:40 AM, three staff members lifted her onto a bed. Upon physical examination she was noted to have labored respirations, a blood pressure palpable at 60 mm of mercury and a weak and irregular pulse. Cardiopulmonary resuscitation was begun five minutes later. The first cardiac tracing, at 6 AM, showed asystole, which failed to respond to the usual advanced cardiac life support, and the patient was pronounced dead at 6:16 AM, 11 hours after ingestion of the drug.

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
TCA = tricyclic antidepressant

Autopsy findings were unremarkable except for the presence of hyperinflated lungs with sputum in the airways. This might have been caused by bronchial asthma, but the obstruction was not significant. The brain and heart were normal in all respects upon both gross and microscopic examination. The liver had some fatty metamorphosis. Analysis of a postmortem blood sample for all the drugs previously listed as well as for alcohol, showed only 8.6 μg per ml (8,600 ng per ml) of desipramine. Plasma levels of 1,000 ng per ml or more have been correlated with coma, seizures, arrhythmias, cardiac arrest and death.[1] A toxicologic test of the urine was negative for opiates, cocaine, amphetamines, methadone and propoxyphene.

Discussion

Delayed Complications

This case illustrates two of the major pitfalls in managing TCA overdose, particularly in an emergency department: delayed complications and inability to predict outcome by early clinical signs. Delayed complications may occur hours to days after ingestion of the drug, even after significant clinical improvement. The literature contains a number of such cases. Two infants who were admitted with coma and seizures, later awakened, and then collapsed and died 12 hours and 48 hours after TCA ingestion.[2,3] Reports of two young adults who were in coma when first examined are also interesting. One awoke and was alert for 12 hours after physostigmine was administered, then went into coma and a heart rate of 180 developed. The other awoke and responded to commands, but went into coma and a supraventricular tachycardia developed 57 hours after ingesting TCA's. Both survived.[4] Of two adults in coma when examined, one awoke and had a pulse rate of 90 per minute with a normal ECG except for incomplete right bundle branch block, yet at 50 hours after ingestion of TCA the patient collapsed, atrioventricular block and electromechanical dissociation developed and the patient died. The other patient not only awoke, but had a pulse rate of 82 per minute and a completely normal ECG, and was alert and cooperative when transferred to the ward. This 21-year-old collapsed on the toilet 94 hours after ingesting the drug, had a very slow heart rate with block and died. Autopsies of both patients were unremarkable.[5] Three other patients were admitted to hospital with major complications, had a cardiac arrest in the first 12 hours after admission but then died much later of other complications such as pneumonia.[6] Half of the patients in one large series had recurrence of tachycardia at 18 to 36 hours[7] and Sedal noted that half his TCA-overdose patients still had tachycardia on the sixth day after ingestion.[5] Most reviews note similar persistence of signs and symptoms, as well as an occasional worsening of the clinical condition after initial improvement.[7-11]

Causes of Delayed Complications

Delayed complications in TCA overdose may be due to several causes. The anticholinergic effects of these drugs slow peristalsis and absorption from the gut in overdose; intact pills have been recovered by lavage up to 18 hours after ingestion.[12,13] Absorption of TCA from the gut is dependent on the pH of intestinal contents; acid conditions hinder absorption.[14] Administration of cathartics may theoretically increase absorption by moving the drug through the alkaline small bowel, although this has never been studied. Once absorbed, the TCA is widely bound to tissue, creating a huge reservoir. Excretion is by renal and enterohepatic routes and is not only very slow but is affected by barbiturates, alcohol and smoking. Metabolism and half-life of these drugs is so variable that plasma levels vary up to 40-fold among persons receiving a given dose. This is among the largest of such differences known for any drug.[14,15] Half-life in overdose varies from 25 to 96 hours, with toxic levels persisting and often fluctuating for several days.[16,17] TCA protein binding fluctuates greatly with pH changes, including those induced by ventilatory status. Binding decreases from 98 percent at a pH of 7.5 to 90 percent at a pH of 7.0, drastically increasing supplies of the pharmacologically active drug. Arrhythmias induced by TCA's at a pH of 7.3 disappear promptly and completely when pH is raised to 7.5 by hyperventilation or administration of sodium bicarbonate.[18]

Predictive Factors

The second dilemma in TCA overdose is that the present state of the art does not allow physicians to predict which patients will have delayed

complications. As the case presented here vividly illustrates, initial absence of significant signs of poisoning such as coma, seizures, arrhythmia or hypotension does not rule out their later, unexpected development. Information about ingested doses is not only hard to obtain and unreliable, but also useless. Some patients have survived ingestion of 10 grams of amitriptyline while others have succumbed to 500 mg.[19,20] QRS duration of more than 0.10 seconds correlates well with plasma levels and major complications, and the general pattern is that the more prolonged the QRS, the higher the plasma level and the sicker the patient.[1] However, 25 percent of normal persons will have a QRS duration of 0.10 seconds and QRS duration has no predictive value, because it can change from minute to minute in concert with acid-base changes.[18] TCA plasma levels can be obtained, and they correlate with major complications.[1] However, this case illustrates also that unlike many other overdoses where relatively steady and predictable blood levels can be measured, plotted out on nomograms and used to predict toxicity, TCA levels can fluctuate greatly. For this reason, plasma levels of the drug have no predictive value. Rather than confirming or ruling out large ingestions, they serve only to document plasma levels at a given moment.

Significance of the Problem

The physician is thus left with no reliable means of predicting the outcome of the patient with only trivial signs of TCA poisoning. The case presented here is the first reported in the literature of an unexpected late death in a patient who initially had only trivial symptoms and signs; in the other six cases in the literature there were major complications such as coma and seizure which led to hospital admission. Conversations with other physicians have revealed several similar cases, and the true incidence of death is unknown. (Readers with experience of similar cases are invited to communicate details to the author.)

In one recent study, 40 percent of all TCA overdose patients had only minor symptoms, 73 percent of pediatric cases had symptoms too minor to warrant treatment and 40 percent of pediatric cases had no symptoms at all.[21] In recent years, 2,657 emergency visits involving amitriptyline alone, and 340 deaths in which amitriptyline contributed, were reported each year for the 30 percent of the United States population monitored by the Drug Abuse Warning Network (DAWN).[22] Thus, thousands of patients each year are seen in emergency departments with only trivial symptoms from TCA overdose, and decisions about their need for admission to hospital must be made.

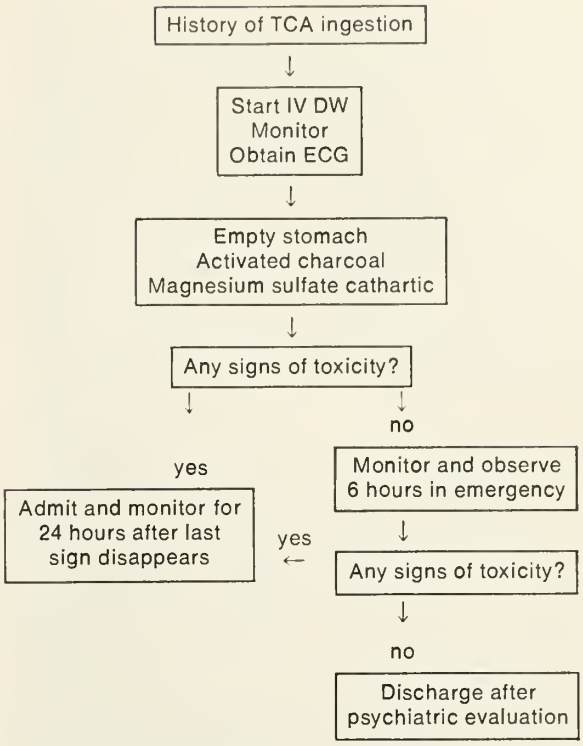

Figure 1.—Initial management strategy in tricyclic antidepressant ingestion.

Suggested Admission Criteria

Definition of the admission criteria for these "minor" ingestions has seldom been addressed in the literature. Rumack recommended that patients without tachycardia (defined as a rate of 110 per minute or greater) or "other life-threatening problems" not be admitted.[23] Such a guideline would not lead to the admission of patients such as this one. Crome and Newman suggested that patients with a history of TCA ingestion, but no symptoms, be observed in the emergency department for six hours and then discharged if still symptom-free.[21] The initial tachycardia of the patient reported here would have qualified her for admission under these criteria.

The protocol recommended by the author is summarized in Figure 1. All patients giving a history of TCA ingestion of any kind should receive an intravenous line at a keep-open rate, have cardiac monitoring done and receive an ECG in addition to the regular physical examination.

They then should have stomachs emptied and receive activated charcoal, which binds the drug in the gut. Repeated doses of charcoal at one-hour intervals bind the portion of the drug excreted in the bile and gastric juices and are even more effective.[24] This important measure was omitted in this patient, and might have prevented the later fatal absorption of the drug. Cathartics are routinely recommended, although their effectiveness has never been studied in any overdose, and they might theoretically increase absorption.[25] Considering the long time the drug may remain unabsorbed in the hypotonic gut, however, it seems logical to bind it with a dose of charcoal and then hasten elimination with cathartics. This step also was omitted in this patient's care.

If on first examination patients have *any* of the signs of toxicity listed in Tables 1 through 3, they should immediately be admitted to hospital. Tachycardia and QRS prolongation are particularly important signs. Most of the less severe of these signs have been reported occasionally as a side effect of therapeutic TCA doses, so acute overdose may be harder to diagnose in those patients receiving ongoing therapy. However, the incidence of side effects is not high enough to create confusion in most cases and when in doubt the patient should be admitted. In the hospital, the patient should be monitored electrocardiographically for at least 24 hours after the disappearance of the last sign because 98 percent of all signs of cardiotoxicity appear within that time period.[23,26] If patients have no signs of toxicity on arrival in the emergency department, they should be monitored and observed for at least six hours. If any signs or symptoms develop, no matter how minor, they should be admitted. If not, they may be discharged after appropriate psychiatric consultation.

This protocol should result in the admission of virtually all potentially fatal cases to the hospital, where cardiotoxicity can be detected early and treated aggressively. It will also result in the admission of a number of trivial cases that do not really need such care. However, the consequences of missing those few who truly need admission are so disastrous that until the true incidence of delayed complications in "trivial" overdoses can be accurately determined, or until accurate predictors of outcome are developed, a very low-risk strategy should be employed.

TABLE 1.—*Peripheral Signs of Tricyclic Antidepressant Toxicity (Peripheral Anticholinergic Syndrome)*

Tachycardia (100 or greater)*
Hypertension
Fever
Mydriasis
Dry red skin
Decreased bowel sounds
Urinary retention
Respiratory depression

*In a quietly resting patient, a pulse rate of 90 per minute or greater should be considered suspicious.

TABLE 2.—*Central Nervous System Signs of Tricyclic Antidepressant Toxicity*

Disorientation
Agitation
Hallucinations
Myoclonic jerks
Coma
Seizures
Pyramidal signs
clonus
Babinski present
hyperreflexia

TABLE 3.—*ECG Abnormalities in Tricyclic Antidepressant Overdose*

ST and T wave changes
Prolonged QT interval
Prolonged PR interval
QRS greater than 0.10 seconds*
Bundle branch blocks
Atrioventricular conduction blocks (first degree, second degree or complete)

*Correlated with high plasma levels and major complications.

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Hypervitaminosis A

A Cause of Hypercalcemia

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In the present climate of increased health and nutrition consciousness, physicians commonly see patients taking a host of different vitamin and mineral supplements, frequently in pharmacologic doses. One lipid soluble vitamin still available in large unit doses and in widespread use is vitamin A. Complications of hypervitaminosis A have been recognized for a number of years. However, hypervitaminosis A has been infrequently recognized as a cause of hypercalcemia. We wish to report the case of a patient who had pronounced hypercalcemia, rapidly reversible after discontinuation of large doses of vitamin A.

Report of a Case

A 29-year-old woman, a part-time employee of a health food store, presented with a four-week history of illness. She had consulted an ophthalmologist for dryness and irritation of her eyes, which prevented her from wearing contact lenses. She also noted redness and irritation of her gums and tongue, and fissures at the corners of her mouth (cheilosis). There was dryness and itching of her skin, as well as generalized weakness and malaise for approximately two weeks. Headache had begun one week before admission, it was occipital in location and moderately severe. She was forced to give up jogging because of muscle aches and pains, particularly in the anterior lower legs. Nausea, vomiting and pronounced weakness had been present for four to five days before her presentation.

Medications

On questioning, it was found that she had taken two tablets per day of a combination vitamin preparation, which contained 25,000 units of vitamin A and 100 units of vitamin D. She had taken two tablets per day for at least three months.

Thinking her dry eyes and mouth may be a manifestation of vitamin A deficiency, she took an additional 50,000 units of vitamin A a day for one week before presentation. She was taking no other medications. Specifically, there were no other sources of vitamin D, calcium supplementation or diuretics.

Physical Examination

The patient appeared moderately ill and weak. Height was 161 cm, weight 52.7 kg. Temperature was 37°C, pulse 52 and blood pressure 110/70 mm of mercury, with no orthostatic drop. There was cheilosis around the mouth and some erythema of the gums and mouth. There was no visible keratoconjunctivitis. The thyroid was normal in size. Findings on examination of the lungs, heart, breasts, abdomen and pelvis were within normal limits. The abdomen was soft. Liver span was approximately 8 cm. There was no palpable splenomegaly. The deep tendon reflexes were symmetrical and normal in timing.

Laboratory Data

The serum calcium concentration was reported to be notably elevated at 14.4 mg per dl. The serum phosphate level was 3.6 mg per dl. Other laboratory data included a leukocyte count of 4,500 with normal differential. Hemoglobin was 10.9 grams per dl. Hematocrit was 30.6 percent. Erythrocyte sedimentation rate was 43 mm per hour. Serum creatinine was 0.9 mg per dl. Pro-

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thrombin time was 12.9 seconds with a control of 11.8 seconds. The serum sodium concentration was 142, potassium 3.9, chloride 112 and bicarbonate 24 mEq per liter. Serum aspartate aminotransferase (previously designated SGOT) was 101 and alanine aminotransferase (previously SGPT) was 50 IU per liter. Hepatitis-B surface antigen was negative. The 24-hour urinary calcium value was 454 mg. Creatinine clearance was 72 ml per minute. The thyroxine value was 4.8 μg per dl, thyroid stimulating hormone 4 μU per ml and triiodothyronine resin uptake 28.2 percent. The vitamin A level was 923 IU per dl (normal 65 to 275). The level three days after the patient stopped taking vitamin A had fallen to 610 IU per dl. The value for 25-hydroxy-vitamin D was 23 ng per ml (normal 10 to 55). An x-ray study of the chest and serum protein electrophoresis showed no abnormalities. Parathyroid hormone was appropriately suppressed at 10 μl equiv per ml (normal 10 to 80), with a concomitant serum calcium level of 15.2 mg per dl. No abnormalities were seen on x-ray films of the cervical spine, hands and tibia.

Hospital Course

The patient was treated with large doses of intravenously given saline for approximately 72 hours. The serum calcium concentration fell promptly (see Table 1). Symptoms of nausea, bone pain and headache disappeared rapidly in two to three days. Weakness and dry mouth persisted for approximately seven to ten days. Serum aspartate aminotransferase appeared to be falling after approximately ten days. Serum magnesium rose spontaneously upon resumption of regular diet. She was followed as an outpatient for two months after ingestion of vitamin A, and has remained normocalcemic.

Discussion

Hypervitaminosis A has been recognized as a potentially serious cause of illness for many years. The major side-effects include hepatocellular damage, which has led to fatal portal hypertension on occasion,[1,2] increased intracranial pressure, and gastrointestinal, cutaneous and musculoskeletal symptoms.[3] Hypercalcemia has been reported only rarely, and approximately seven patients have been described previously.[3-7] The minimum dose of vitamin A required to produce toxicity, particularly hypercalcemia, cannot be stated with certainty. The majority of patients have ingested 50,000 units per day or more for a prolonged period of time. The recommended daily allowance as established by the Food and Drug Administration at present is 5,000 IU per day. Nevertheless, despite its potential toxicity, vitamin preparations containing much larger amounts continue to be available without prescription.

Symptoms seen after ingestion of a single large dose of vitamin A are abdominal pain, nausea, vomiting, dizziness, sluggishness and irritability. Spontaneous recovery is usually seen.[3] In the early stages of chronic ingestion, vitamin A is stored in the liver and serum levels are low. When the storage capacity of the liver is exhausted, serum levels rise. Hypervitaminosis A causes symptoms referable to multiple organ systems. Of all the symptoms, hypercalcemia is reported rather infrequently.[3-7] In the published case reports, the range of hypercalcemia has been anywhere from 12 to 18.9 mg per dl. The calcium

TABLE 1.—*Change in Serum Calcium and Liver Enzymes After Stopping Vitamin A*

Date	*Calcium (mg/dl)*	*Phosphate (mg/dl)*	*Parathyroid Hormone (μl equiv/ml)*	*Aspartate Aminotransferase (IU/liter)*	*Magnesium (mg/dl)*	*Vit. A (IU/dl)*	*Alanine Aminotransferase (IU/liter)*	*Urinary Calcium (mg/24 hr)*	*Creatinine Clearance (ml/min)*
9/ 3/80	13.4	..	10*	...	..	...	..	...	..
9/ 5/80	14.4	..	..	...	..	923	..	...	..
9/ 6/80	11.3	..	..	...	..	...	..	...	..
9/ 7/80	10.2	..	..	...	..	...	..	...	..
9/ 8/80	10.8	3.6	..	103	0.8	610	50	454	80
9/ 9/80	10.0	..	..	...	..	...	..	...	..
9/10/80	11.0	..	..	111	1.4	...	62	...	..
9/11/80	11.0	..	..	...	..	...	..	...	..
9/12/80	11.1	..	..	...	..	...	..	...	..
9/16/80	10.1	..	..	85	..	...	44	...	..
10/13/80	8.4	..	..	...	..	...	..	...	..

Aspartate aminotransferase previously was designated SGOT and alanine aminotransferase was SGPT.

*Normal 10-80 μl equiv per ml.

level is reported to decrease within one day of hydration, and to reach normal ranges within ten days to a month. This was the case in our patient.

The mechanism of hypercalcemia in hypervitaminosis A remains unclear. Vitamin A probably acts directly on bone, causing stimulation of osteoclastic resorption or inhibition of osteoblastic formation, or both.[8] Fractures and modeling defects of long bones with increased bone resorption have been reported to occur in rats after a daily dose of 50,000 units of vitamin A for one week.[9] In tissue cultures, direct application of vitamin A acetate to mouse parietal bone caused focal bone resorption.[10] Characteristic periosteal calcifications have been reported in several patients with chronic ingestion. In our patient parathyroid hormone levels were suppressed as would be expected in a non-parathyroid hormone dependent form of hypercalcemia. In the case reported by Weiland and co-workers, the patient had normal parathyroid glands at surgery.[6]

Our patient had another manifestation of hypervitaminosis A: abnormal liver function. Hepatocellular damage, portal fibrosis and cirrhosis have been reported and are probably related to large deposits of vitamin A in the liver.[1,2,11] Liver biopsy studies have shown perisinusoidal fibrosis, central vein sclerosis and focal congestion associated with perisinusoidal lipid storage cells called Ito cells. Obliteration of Disse's spaces by Ito cells has been reported. Electron microscopy showed increase in basement membrane-like material and collagen within the perisinusoidal space in association with Ito cells.[2] These changes may obstruct hepatic blood flow, cause parenchymal cell atrophy and lead to portal hypertension.

Summary

In summary, we have reported a case of hypercalcemia resulting from hypervitaminosis A—an occurrence that has been reported infrequently. The hypercalcemia is easily treatable. Physicians should be aware of hypervitaminosis A causing hypercalcemia. In view of heightened public interest in vitamin A, hypervitaminosis A may become a greater problem in the future. All patients should be carefully questioned regarding vitamin and food supplements (information not usually included in medical histories). Considerable effort may be required to obtain this information. As has been emphasized previously, prohibition of direct marketing of doses of vitamin A in the pharmacologic amounts could help to decrease this potentially serious complication.[12] Additional public and physician education regarding potential toxicity of doses of vitamins far in excess of recommended daily allowances would help to reduce this public health hazard.

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Survival After Intracerebral Hemorrhage in Wegener's Granulomatosis

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WEGENER'S GRANULOMATOSIS has been well known since its original description in 1936[1] as a necrotizing granulomatous vasculitis involving upper and lower respiratory tracts as well as the kidneys. Since that time the systemic nature of the illness with involvement of virtually all organ systems has been stressed.[2] Drachman first emphasized the neurologic complications of the ill-

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ness in 1963 when he noted them in 56 of 104 reported cases.[3] He described three subsets of neurologic complications. The first included central nervous system encroachment from contiguous nasal and paranasal granulomas. The second included direct granulomatous involvement of the peripheral and central nervous system. The third included vasculitis of the nervous system. Most of the latter subset involved vasculitis of the vasa vasorum with production of polyneuritis and mononeuritis multiplex. Cerebral vasculitis has been seldom reported and is usually fatal.[4,5] We recently observed a case of Wegener's granulomatosis, complicated by intracerebral hemorrhage, that resolved on cytotoxic therapy. This case is described below with a review of the occurrence of cerebral hemorrhage in Wegener's granulomatosis.

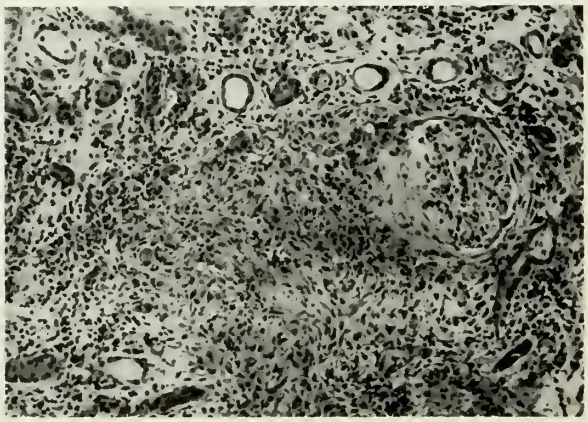

Figure 1.—Crescentic glomerulonephritis shown by light microscopy. Glomerulus reveals large epithelial crescent obliterating Bowman's space and compressing glomerular capillary tufts. Hypercellularity of glomerulus is consistent with mesangial proliferation. (Reduced from ×300, hematoxylin-eosin stain.)

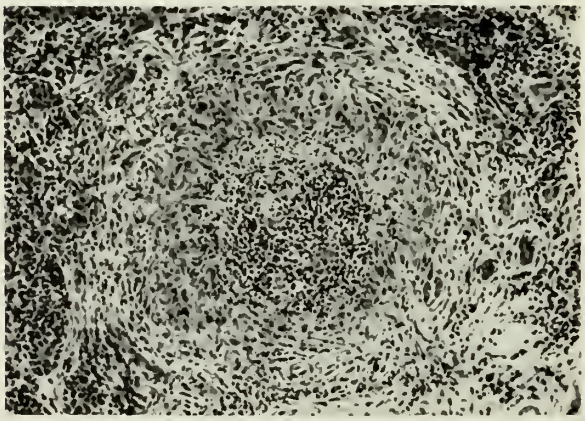

Figure 2.—Granulomatous vasculitis shown by light microscopy. This histologic section of the kidney shows an inflammatory infiltrate surrounding a medium size vessel, consistent with vasculitis. Also noted in the infiltrate are several giant cells. No caseation was seen. No eosinophils were seen. (Reduced from ×450, hematoxylin-eosin stain.)

Report of a Case

The patient, a 57-year-old white woman, was in normal health until August 1979 when she noted arthralgias of her ankles. She sought evaluation at another hospital in May 1980, at which time cavitating pulmonary infiltrates were noted incidentally on a chest roentgenogram. Renal function as assessed by analysis of urine, serum creatinine and blood urea nitrogen was normal. A percutaneous lung biopsy was done for evaluation of the pulmonary lesions and showed caseating granulomas which were culture negative for acid-fast bacillus and fungi. The patient was referred to our institution in August 1980 for further evaluation of the pulmonary lesions.

Upon admission the patient was alert and oriented but appeared chronically ill. Blood pressure was 120/80 mm of mercury, pulse rate 120 per minute, temperature 36.9°C, respirations 20 per minute and weight 60 kg. Results of examination of head, eyes, ears, nose and throat were unremarkable. The lungs were clear to auscultation and percussion. On cardiovascular examination, an S4 gallop and bilateral femoral bruits were noted. No abnormalities were found on breast, abdominal, and pelvic examinations. Multiple subcutaneous nodules on the hands and painful range of motion of the ankles without swelling or erythema were noted. Findings on neurologic examination were normal.

Laboratory Data

The hematocrit was 27.2 percent, leukocyte count 8,600 per cu mm and platelet count 877,000 per cu mm. The prothrombin time was mildly prolonged at 16.2 seconds with a control of 13 seconds. The partial thromboplastin time was normal. The zeta erythrocyte sedimentation rate was moderately elevated at 55 units. Analysis of urine showed specific gravity 1.010, pH 5.0, protein 3+, hemoglobin 3+, erythrocytes 3+ and leukocytes 1+. No granular or erythrocyte casts were observed. The blood urea nitrogen and serum creatinine values were 128 and 5.8 mg per dl, respectively. A 24-hour urine creatinine clearance and protein values were 10 ml per minute and 1.1 grams, respectively. A roentgenogram of

the chest showed multiple cavitating parenchymal densities.

Hospital Course

Because Wegener's granulomatosis was suspected, an open renal biopsy was carried out. Light microscopy showed crescentic glomerulonephritis with granulomatous vasculitis consistent with Wegener's granulomatosis (Figures 1 and 2). Immunosuppressive therapy was begun, consisting of 60 mg of prednisone and 125 mg of cyclophosphamide per day given by mouth.

Seven days after initiation of chemotherapy, before any evidence of pulmonary or renal response, the patient complained of a severe frontal headache, blurred vision and vomiting. She was seen to have a generalized tonic-clonic seizure. Physical examination at this time found blood pressure of 150/90 mm of mercury, nuchal rigidity and disorientation without focal neurologic deficits. The platelet count was 382,000 per cu mm and the prothrombin time and partial thromboplastin time were unchanged. A computerized tomographic scan of the head showed an area of increased density along the anterior interhemispheric fissure (Figure 3). On a lumbar puncture the following findings were noted: an opening pressure of 30 cm of water, xanthochromic fluid, 3,310 erythrocytes per cu mm, 4 leukocytes per cu mm, glucose 89 mg per dl and protein 30 grams per dl. A cerebral angiogram was normal. The patient's condition was stabilized with phenytoin (Dilantin) given intravenously, dexamethasone (Decadron) and antihypertensive therapy.

Forty-eight hours after the acute episode, she was alert and oriented with normal neurologic findings. Repeat roentgenogram of the chest showed an interval improvement although the values of blood urea nitrogen were complicated by a perforated gastric ulcer from which the patient recovered completely. She was discharged in good condition on the 30th hospital day.

Long-term Follow-up

At the time of this writing the patient is alive and well six months after her presentation with cerebral hemorrhage. She is receiving 1 mg per kg of body weight per day of cyclophosphamide

Figure 3.—Computerized tomogram of the head showing an area **(arrow)** of increased density along the anterior interhemispheric fissure compatible with hemorrhage.

TABLE 1.—*Data on Seven Patients With Cerebral Hemorrhage Complicating Wegener's Granulomatosis*

Case No.	*Reference*	*Age (yr) and Sex*	*Time from Initial Presentation with Pulmonary or Renal Disease to the Diagnosis of Cerebral Hemorrhage*	*Medical Therapy*	*Course Clinical*	*Clinical or Pathologic Findings*
1	Tuhy et al[9]	39 ♂	3½ months	None	Fatal	Subarachnoid hemorrhage
2	Tuhy et al[9]	46 ♂	4 months	Corticosteroids	Fatal	Intracerebral hemorrhage
3	McFadyen[10]	42 ♂	3½ months	Corticosteroids	Fatal	Thalamic hemorrhage and necrotizing cerebral angiitis
4	Kinney et al[11]	55 ♂	4 months	Corticosteroids	Fatal	Massive cerebral infarction and hemorrhage
5	Rordon et al[12]	53 ♂	5 years	Corticosteroids and mercaptopurine	6 month survival	Subarachnoid hemorrhage*
6	Lucas et al[5]	53 ♂	1 month	Corticosteroids	Fatal	Intracerebral hemorrhage and necrotizing cerebral angiitis
7	Present Case	57 ♂	4 months	Corticosteroids and cyclophosphamide	Alive at 6 months	Intracerebral hemorrhage

*The patient died six months later from an intracerebal hemorrhage.

by mouth. Pulmonary infiltrates have resolved and the creatinine value has improved to 2.9 mg per dl. Neurologic findings remain normal.

Discussion

Our patient presented with the clinical findings, cerebrospinal fluid characteristics and computerized tomographic evidence of an intracerebral hemorrhage four months after she was found to have pulmonary granulomatous disease. Intracerebral hemorrhage has been described with systemic vasculitides. In the absence of antecedent trauma or hypertension, angiographic evidence of aneurysm or vascular malformation, blood dyscrasia or significant coagulopathy, we may assume that the hemorrhage was secondary to the same necrotizing vasculitis that involved her kidneys and lungs.[6] The hemorrhage occurred eight days after initiation of therapy with cyclophosphamide and before evidence of pulmonary or renal improvement. Because the effects of cyclophosphamide are not seen for approximately 14 days[7] it is not surprising that this therapy did not prevent the cerebral vasculitis. Concomitant improvement of neurologic status and roentgenographic healing of her pulmonary cavities suggested to us that the therapy may have succeeded, however, in terminating the episode of cerebral vasculitis.

Although neurologic involvement in Wegener's granulomatosis is reported to be as high as 54 percent,[3] cerebral vasculitis is rare. Drachman recorded only four cases of cerebral vasculitis in his review of 104 cases of Wegener's granulomatosis. Anderson and co-workers, in a recent review of 249 cases, found only 11 cases of cerebral vasculitis.[8] Of the 11 cases, 5 were characterized by intracerebral or subarachnoid hemorrhage. Since that review only one case of cerebral vasculitis and hemorrhage complicating Wegener's has been reported.[9] The characteristics of these seven cases along with our case are included in Table 1.

Cerebral hemorrhage occurred from one month to five years after these patients presented with pulmonary or renal involvement. The hemorrhage was rapidly fatal in the one patient who received no treatment. Interestingly, the four patients treated with corticosteroids alone also had a rapidly fatal course. Rordam and Hansen reported a case of Wegener's granulomatosis in which the patient recovered from a subarachnoid hemorrhage while being treated with the combination of steroids and mercaptopurine.[12] That same patient died six months later from a massive cerebral hemorrhage. Our patient also survived her initial episode while being treated with a combination of agents.

We conclude that cerebral vasculitis is a rare complication of Wegener's granulomatosis, occurring in less than 5 percent of one large series of patients. Cerebral hemorrhage is not uncommonly the manifestation of cerebral vasculitis. This appears to be a late and rapidly fatal complication that responds poorly to corticosteroid therapy alone. Our patient, who was treated with a combination of corticosteroids and cyclophosphamide, survived the initial hemorrhage. Furthermore, there was no evidence of cerebral vasculitis six months later, while receiving a maintenance regimen of cyclophosphamide. With the early recognition of Wegener's granulomatosis and prompt institution of cytotoxic therapy this complication may be avoided or have a self-limited course as illustrated by the case presented. Long-term treatment with cytotoxic therapy appears warranted in a patient who survives an initial episode of cerebral hemorrhage due to cerebral vasculitis.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Differential Diagnosis of Pleural Effusions

To the Editor: The journal continues to publish very stimulating material. In one excellent recent article, Sahn discussed the enormous amount of information that can be gleaned from the analysis of pleural fluid.[1] He, however, did not consider an important test that occasionally provides the only clue to the diagnosis of malignant disease of the pleura: cytogenetic analysis of the cells in the pleural fluid. We believe that this test is important and deserves comment.

Malignant disease involving the pleura produces a variety of chromosomal abnormalities in the cells of the pleural effusion. Among these, hyperdiploidy and the presence of abnormal marker chromosomes have been suggested as useful criteria for the diagnosis of malignancy.[2] In one series,[2] routine cytologic examination could identify 65 percent of malignant effusions whereas cytogenetic analysis correctly diagnosed around 70 percent of such effusions. The difference between these figures was not statistically significant. However, when the results of the two tests were analyzed together, 83 percent of malignant effusions could be correctly identified, a result that was superior to either test done alone. Interestingly, cytogenetic analysis correctly identified more than 85 percent of lymphoma and leukemia involving the pleura, while cytologic examination could show only about 30 percent, a significant difference.

What is important about chromosomal analysis of pleural fluid is that it may be the only positive feature in an otherwise negative battery of tests done on the pleural fluid. Dewald and associates described three of several such patients in whom the typical chromosomal changes of malignancy were the only positive findings.[2] These patients subsequently manifested overt malignant disease; in one of the patients malignant mesothelioma developed six months later. Cytogenetic examination may therefore provide an early clue to the diagnosis of malignant disease of the pleura. Furthermore, it is inexpensive,[3] easily performed in any genetic diagnostic laboratory[2] and can provide a diagnosis as early as five hours[1,2] after the pleural tap.[2] In view of these advantages and in order to ensure that physicians consider chromosomal analysis of pleural fluid, it must be included among the routine tests done to ascertain the etiology of pleural effusions.

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* * *

To the Editor: Dr. Sahn has written an informative and almost comprehensive article on the differential diagnosis of pleural effusions, which was published in the August 1982 issue.[1] No article on this subject is complete, however, without at least mention of two additional diagnostic techniques, thoracoscopy and open pleural biopsy. We have found these procedures to be most useful in establishing the diagnosis of a malignant pleural effusion when cytology of the pleural fluid has been negative and when needle biopsy of the pleura has been negative as well. Sahn points out that pleural fluid cytology is positive in "approximately 50 percent to 70 percent of patients" and "the yield of repeat cytology in carcinoma of the pleura is 17 percent to 22 percent." He goes on to say that "carcinoma may be diagnosed on pleural biopsy in approximately 60 percent of cases of carcinoma of the pleura." A number of patients remain who have pleural malig-

nancies which have not been diagnosed by these relatively simple techniques.[2]

In such instances our next step would be thoracoscopy, a procedure which is done under general anesthesia but which results in little risk or discomfort for the patient.[3] We use a double-lumen endotracheal tube for administering anesthesia in order to allow for collapse of the lung on the involved side thereby enabling the surgeon to get a thorough look at the pleural cavity. Biopsy is then performed under direct vision, and with safety. Using this technique we have been able to diagnose accurately all pleural effusions due to carcinoma in which pleural fluid cytology and pleural biopsy have been negative.

In some cases of nonmalignant pleural disease, and especially in patients with malignant mesothelioma, open pleural biopsy through a limited thoracotomy incision has been necessary to establish the diagnosis. The diagnosis of malignant mesothelioma is occasionally very difficult to establish short of providing the pathologist with a generous pleural biopsy specimen. When either of these techniques is used tetracycline can be instilled into the pleural cavity at the time of the procedure when the diagnosis of malignancy has been established thereby saving the patient the discomfort of this instillation at a different time.

Dr. Sahn is well-known for his expertise in pleural physiology and his article in the August issue is an excellent one. I mention these two invasive procedures only for the sake of completeness because I believe, as I am certain Dr. Sahn does, that the cause of a pleural effusion should be established with certainty whenever possible.

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AMA and a National Health Policy

To the Editor: I enjoyed reading your editorial[1] in the August 1982 issue about the project "Health Policy Agenda for the American People." As Chairman of the Steering Committee of this AMA-initiated project, I am pleased with the number of articles and letters supporting the Health Policy Agenda.

However, there is one item in the editorial that I wish to correct. After the draft proposal was presented to the AMA House of Delegates in June 1982, the Steering Committee approved the addition of representatives from the Department of Health and Human Services, the Department of Defense and the Veterans Administration on the Steering Committee and on certain work groups. The National Conference of State Legislatures and the National Governors' Association are represented on the Advisory Committee.

Your editorial was excellent and thank you again for the support of this important project.

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Ascaris Infection in Washington State

To the Editor: Pig manure, used as a fertilizer for vegetable gardens, is becoming increasingly popular among organic gardeners in Washington state. This popularity has resulted in large part from the increased price and decreased availability of cow manure. However, recent reports of *Ascaris* transmission from pigs to humans suggest that this practice may increase the risk of *Ascaris* infection.[1,2] To investigate the association of exposure to pigs or pig manure with infection, a survey of Washington state residents with laboratory confirmed *Ascaris* infection was conducted.

Over an 18-month period from January 1981 through June 1982, there were 328 cases of *Ascaris* infection identified by the Washington State Public Health Laboratory. Of these, 71 percent occurred either in Asian refugees or other recently arrived aliens, 22 percent in migrant farm workers and 8 percent (25 people) in US citizens who were not farm workers.

The survey was limited to 23 people who were US citizens and had resided in Washington state for one year before diagnosis. Of the 23 people, 18 reported extended exposure to pigs (pigs, pig manure or old pig sties). Five of the people reported out-of-state travel; however, three of these also reported exposure to pigs in Washington state. One of the five traveled to Central America. There were 14 of the 23 people (61 percent) under 4

years of age. Eighteen controls were matched to cases on the basis of age, sex and county of residence. Controls were selected from *Ascaris*-negative people routinely interviewed for *Giardia* or *Campylobacter* infection. None of the controls reported exposure to pigs or pig manure.

Although *Ascaris* infections are usually asymptomatic, complications such as pneumonia or intestinal obstruction can occur. Since *Ascaris* occurs commonly in pigs, people who have pigs or who use pig manure should take precautions to avoid infection. Exposure to pigs should also be considered where other likely sources of *Ascaris* infection cannot be found.

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Usefulness of IDA Scanning

To the Editor: As a surgeon, I must agree with Krishnamurthy[1] (in the August 1982 issue) that IDA scans are a useful adjunct in the evaluation of patients with right upper quadrant pain. However, one must avoid a tautological trap in assuming that abnormal scan findings equal acute cholecystitis. The latter must be differentiated from such varied entities as perforated ulcers, leaking aortic aneurysms, pleurisy and myocardial infarctions.[2] Coexistent cystic duct obstruction has been found with these and many other disorders.

The accuracy and inaccuracy of IDA scanning, especially in chronic cystic duct obstruction, has been documented.[3,4] Although Dr. Krishnamurthy has attempted to display the relative effectiveness of IDA scanning over other noninvasive methods by bayesian analysis, his data and the clinical condition of his patients have not been presented. Since acute cholecystitis is ultimately a pathological diagnosis, which of these patients came to laparotomy? On what basis are false negatives determined if no laparotomy has been carried out?

Although IDA scans provide timely evidence for pathological cystic duct obstruction, not every patient with this condition should undergo immediate cholecystectomy; the dangerous period for increased operative risk in delayed cholecystectomy occurs days, not hours, after the onset of symptoms.[5-9] IDA scans do not obviate a careful evaluation of the patient with right upper quadrant pain, nor should they be used as a rationale for rushing an ill-prepared patient to surgery.

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Nuclear Armaments

To the Editor: The physicians' movement against nuclear weapons has based many of its activities and arguments on a preventive medicine model. It is said that nuclear war is a disease for which there is no cure and therefore the appropriate role of the medical profession is in prevention. This analogy supports the high level of activity on the part of physicians in efforts towards nuclear disarmament. Objectors to this stance generally take exception to either the notion of nuclear war as a medical problem or of medical care as a political activity. Arguments countering these objections are supported by examples from the history and current activities of the field of public health and of clinical preventive medicine.[1]

An article in the August 1982 issue of The Western Journal of Medicine brought yet another example to mind. Chang and Levy[2] describe the significant problem of infant passenger trauma in automobiles, and bemoan the fact that so few parents are made aware of the need for restraining infants in special seats during automobile travel. They conclude that (1) the morbidity and mortality of injuries to infants in automobiles justifies an active concern on the part of physicians and (2) that the two activities most likely to be successful are direct education of

parents by pediatricians and legislation requiring the use of special seats for infants. It is a logical sequence. One looks at the scope of the problem, and the likely sources of successful intervention—education and political action. They state "because child passenger deaths and injuries are the most common cause of death during early childhood, these restraints are logically a priority for preventive education by the medical profession. We cannot inoculate against child passenger injuries; we must educate." The parallel in this language to the nuclear weapons issue is striking. Medical intervention after a nuclear war would be useless. We cannot inoculate; we must educate.

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* * *

To the Editor: Thank you for presenting the editorial "Paranoia and Nuclear Armaments."[1] I would like to correct one factual point, without taking issue with your major point that the paranoid world view of the superpowers is dangerous to life on earth. You mention that there have not been significant antinuclear protests on the other side of the Iron Curtain. There is in fact a vigorous protest movement in Eastern Europe (*Mother Jones*, Sep/Oct 1982), all the more remarkable because of the higher penalties for dissent in this region.

It is interesting that America's mainstream media give virtually no coverage to this movement. In psychological terms, this can be seen as another aspect of the paranoid perspective. A paranoid patient attributes or projects all his unacceptable impulses onto others; the "enemies" are not seen in fully human terms. Similarly, to acknowledge the existence of dissent in Eastern Europe would destroy our image of these countries as part of an inhuman totalitarian monolith. A paranoid patient processes and edits all incoming data to prove or justify his position, just as the US government and media selectively process information about "enemies."

The psychiatric treatment of paranoid patients is especially difficult when reality testing is impaired by fixed delusional beliefs. Antipsychotic medications, which inhibit limbic system activity, are often helpful. In this allegorical case of the United States as patient, some inhibition of the military-industrial system, particularly the nucleus pentagonosus, seems indicated. Several nuclear freeze referenda this fall may prove to have fairly potent suppressive activity in this vital US nerve center.

Psychological treatment aims to minimize denial and projection of the patient's own hostile and aggressive impulses, by providing direct and undistorted feedback to the patient. Thus it is important that accurate data on world events be made available in order to counter widespread paranoid distortions which actually border on fixed delusions (that is, that Russia is the only threat to world peace, that Russia exerts total control over the thoughts and lives of Eastern Europeans and so on).

Your editorial was an important step in this direction; coupled with evidence of dissent in communist bloc countries, it can only encourage us that there is a growing world awareness of the insanity of the nuclear arms race.

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Sherlock in the Emergency Room

To the Editor: "The Bedside Sherlock Holmes" in the August issue[1] contained an enjoyable collection of clinical lore, the more so for neurologists because of our traditional reliance on observation and inference. As the article pointed out, such observations become especially valuable in emergency evaluation of an obtunded patient. In this setting, differentiating new neurologic signs from old assumes critical importance. The article did not mention the value of examining old wallet photos for head tilt (congenital fourth nerve palsy), anisocoria (congenital anisocoria or old Horner's syndrome, rarely old third nerve palsy) or facial asymmetry. Difference in eye color also provides an important tip-off to congenital Horner's syndrome. Postiridotomy pupils must not be inadvertently labeled as asymmetric or unreactive on a neurologic basis. We have also seen

the jiggling of a flaccid, postsurgical iris confused with nystagmus.

The authors mention differential shoe and cuff wear as signs of covert hemiparesis. As with many clinical signs, this one is helpful only when positive. As a companion observation, a hemiparesis —even minimal—which persists from early youth may cause hemiatrophy, which then yields asymmetry of shoe size or sleeve fit. For us, comparing thumbnail size of the two hands provides the most sensitive index. The dominant thumbnail is normally larger by about 1 mm.

Makeup erosion or facial stains can reveal subtle mouth weakness, either bilateral as in myopathy or unilateral as in old hemiparesis or Bell's palsy. The "Cloret sign" is a greenish stain running from mouth to chin noted in a chronic Clorets user who had unilateral drooling due to subtle facial weakness.[2] A variety of similar manifestations can be generated, limited only by the habits of an individual patient. Unilateral inattention to makeup or dressing may result from a contralateral parietal lobe lesion, either subacute or chronic.

In this era of screening chemistry panels and sophisticated imaging technology, it is refreshing to see a reaffirmation of bedside observation as given by Drs. Fitzgerald and Tierney. We hope that other readers enjoyed their "ineffable twaddle" as much as we did.

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Serendipitous Diagnosis of Multiple Myeloma by Hemoglobin Electrophoresis

To the Editor: Wadsworth Medical Center, Los Angeles, participates in the Veterans Administration Sickle Cell Screening and Education Program. Hemoglobin electrophoresis is assayed in all black patients, regardless of age or medical condition. A routine survey resulted in the identification of a patient whose electrophoretic pattern contained an abnormal band that migrated in the opposite direction from all recognized hemoglobin variants. Virtually all hemoglobins migrate anodally from the point of hemolysate application on cellulose acetate at pH 8.4[1]; the patient's band migrated cathodally.

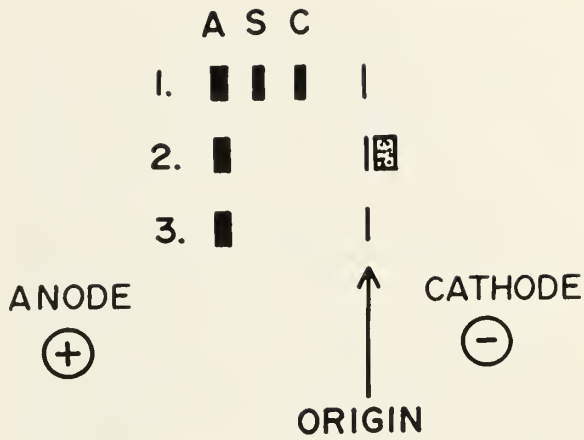

Figure 1.—Schematic representation of hemoglobin electrophoretic patterns. 1. Control containing hemoglobins A, S, and C. 2. The patient's unwashed erythrocytes. 3. The patient's washed erythrocytes. The point of hemolysate application and the electrodes are identified.

This 64-year-old man was admitted to hospital for physical therapy of low back pain. Laboratory studies showed the presence of anemia, mild hypercalcemia and compression fractures of the lumbar spine. An M-spike of 3.5 grams per dl was noted on serum protein electrophoresis and the paraprotein was determined to be IgG_1-λ. Normal immunoglobulin values were slightly decreased and light chains were not detected in the urine. The bone marrow was diagnostic of multiple myeloma. The abnormal band was not visible on unstained preparations, indicating that it did not represent a heme-containing protein. The original hemoglobin electrophoresis was performed on unwashed red cells. After washing the erythrocytes in normal saline, the cathodal band on hemoglobin electrophoresis disappeared (Figure 1). Evaluation of the patient's plasma alone under the conditions of routine hemoglobin electrophoresis demonstrated the abnormal band to be present at the same cathodal location. Thus, the abnormal band seen on hemoglobin electrophoresis proved to be the patient's IgG-λ paraprotein.

The plasma proteins can be seen on hemoglobin electrophoretic patterns,[2] but usually do not confuse the pattern. Most proteins have a negative charge at alkaline pH's and migrate toward the anode. However, cellulose acetate contains large negative charges which fix the positive buffer, resulting in a flow of buffer with some plasma

proteins (such as IgG) toward the cathode when electrophoresis is performed at pH 8.[3]

Hemoglobin electrophoresis is not being advocated as a diagnostic test for multiple myeloma (or as a routine procedure for 64-year-old black men, for that matter). However, the experience reported herein shows that a watchful eye on the part of hemoglobin electrophoresis pattern interpreters may be able to distinguish situations such as the increased hemoglobin A_3 which may accompany lead intoxication,[4] the decreased erythrocyte carbonic anhydrase (which migrates near hemoglobin A_2) associated with thyrotoxicosis,[5] as well as paraproteinemia.

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Leukemia in Hospital Patients With Occupational Exposure to the Sawmill Industry

To THE EDITOR: A recent report by the International Agency for Research on Cancer (IARC)[1] concluded that available data indicate a possible association between exposure to the lumber and wood products industries and hematopoietic and lymphoreticular cancer. Some of the studies reviewed implicated chemicals such as chlorophenols used in the treatment of the wood and phenoxy herbicides used in the forest as possible causal agents. Greene and co-workers[2] also suggested that chemical exposures in the sawmill industries may be related to Hodgkin's disease in workers; Milham and Petersen,[3,4] in studies of death certificates in Washington and California, link a number of cases of lymphatic and hematopoietic cancer to occupational wood exposure; Bross and associates[5] also showed high risks of myeloma to workers in these industries.

A surveillance study in southern Oregon carried out in 1980 by the University of Utah Research Institute and sponsored by the National Institute for Occupational Safety and Health (contract 210-78-0066) obtained results that are consistent with the above findings and are briefly presented here to provide additional insight into these relationships.

TABLE 1.—*Leukemia Cases by Sawmill Exposure and Age Category*

		No. of Cases			*Relative Risk*	
Age	*Group*	*No Exposure*	*<10 Years Exposure*	*≥10 Years Exposure*	*<10 Years Exposure*	*≥10 Years Exposure*
35-54	Case ...	1	1	1	2.0	4.6
	Control .	138	68	30		
55-64	Case ...	2	0	1	0.0	1.7
	Control .	117	51	34		
65-74	Case ...	7	3	4	1.2	2.4
	Control .	158	55	37		
75 +	Case ...	2	1	3	1.2	6.8
	Control .	91	37	20		
Total	Case ...	12	5	9	1.1*	3.2*
	Control .	504	211	121		

Summary x^2 (1 df) = 5.67, P = .017
Case: ICD-9-CM Codes 204-208
Control: ICD-9-CM Codes 001-139, 240-279, 580-611, 740-759, 780-799, 960-999, V01-V82

*Age-adjusted summary relative risk.

The study was undertaken to evaluate the adequacy of hospital records for occupational health surveillance. Brief occupational questionnaires were administered for a year to all men entering four hospitals in Jackson, Josephine and Klamath counties, Oregon, to be used in conjunction with available computerized medical abstract data. Data on 9,612 admissions were collected with a response rate to the questionnaire of 90 percent for the diagnoses reported in Table 1. A control group was chosen composed of patients with a variety of primary diagnoses selected on the basis that they were unlikely to be related to the exposures under study. This control group accounted for 16 percent of the total discharges and was used to evaluate groupings of all remaining diagnoses in a case-control fashion with respect to lumber and wood products exposures.

Neoplasms were one of the groupings evaluated. As a consequence of small numbers of cases, risks of neoplasms for lumber and wood products exposures did not generally show statistically significant increases; however, the highest relative risks for primary diagnoses were for leukemias (ICD-9-CM codes 204 to 208) in patients with sawmill exposure. To increase the numbers, secondary diagnoses were searched, revealing 11 additional cases, with 7 of these having sawmill industry exposure.

Table 1 summarizes the case-control relative risks by years of sawmill exposure separated by age group. A Mantel-Haenszel summary relative risk showed a threefold increase in leukemia risk to patients with ten or more years of sawmill industry exposure, with a Mantel-Haenszel summary x^2 for dose-response statistically significant at $P=.017$. The table excludes patients under 35 for whom very few high exposures were noted and excludes repeat discharges for the same diagnosis. In addition, patients with other types of lumber and wood products exposure are not included in the no-exposure group since these industries are somewhat related to the sawmill industry in terms of work exposures and thus might dilute the risks.

As a check on the adequacy of the control group, the overall study showed statistically significant increased relative risks to lumber and wood products workers for a multitude of musculoskeletal diseases, injuries, hernias, several gastrointestinal conditions and mononeuritis. Overall, about twice as many significant associations as would be expected by chance were found. A National Institute for Occupational Safety and Health study of Social Security disability awards[6] mirrors very closely the musculoskeletal and injury findings, hernias have also been noted by Goldberg[7] and neuritis as an occupational hazard is described by Mayers.[8]

The point of interest is that these data seem to corroborate the IARC findings, using data from a surveillance study in another setting. The increased risk for patients with a sawmill work history, and not necessarily for those with millwork and logging exposures, could be, in part, an artifact of sample size since there were more people with sawmill exposures, but could also be due to specific exposures such as the chemical hazards suggested earlier. For example, industrial hygiene surveys of plants in the study area indicate the use of chlorophenols and even wood dust itself may be suspect.

It should also be kept in mind that the methodology of a surveillance study is less rigorous, with the emphasis on large numbers of patients, many diseases and several exposures, at the expense of the more detailed exposure and disease data that can be collected in smaller definitive studies of one disease and one exposure.

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High Rock, High Tech and Karl Marx

TO THE EDITOR: Another acronym, VDT, is in the news. VDT is not another sexually transmitted disease, nor does it have to do with alcohol withdrawal. As most physicians know, VDT stands for video display terminal.

VDT means excitement, high technology and, most of all, money. John Chancellor, on the evening news, tells the Horatio Alger story of the half a dozen youthful entrepreneurs who have rapidly amassed great fortunes in the computer industry.

There is this 30-year-old genius named Wozniak who used 12 million of his easily earned Apple II computer dollars to stage a "Western Woodstock." In the amphitheater there was a continuous flow of rock music, in an adjacent tent he had a glittering array of sophisticated computerized technology. Video display terminals were there for everyone to play with—high rock wedded to high tech. In the vernacular of the trade we are "on the fast track" to computer culture.

This would seem to epitomize the new and wonderful era on whose brink we now stand. The stodgy old work ethic can be discarded. Thanks to the computer, we can enjoy more and work less. Let the machines do our thinking for us. Grade school kids no longer need multiplication tables or long division. At ready are their handy pocket calculators. Doctors can call on their computers for a quick diagnosis and the proper treatment protocol. No more head-scratching. No more soul-searching. Should it be that a mistake was made and the patient dies, let them sue the computer. High rock and high tech and a VDT in every office and every kitchen—the dream of tomorrow.

But there are dark clouds on the horizon. An

article in a Washingtan state newspaper carries the headline "VDT Horror Stories arc Scaring Workers" (*Spokesman-Review* [Spokanc, Wash], Aug 23, 1982). The story goes on to say that "Of six pregnant women who worked at video display terminals (VDTs) on their jobs at Vancouver's Surrey Memorial Hospital, only one gave birth to a healthy baby." Two women had miscarriages, one infant was a month premature, one baby had a deformed foot and one had a "serious lung condition." This can, of course, be considered purely coincidental. Yet everyone knows that the cathode tubes in VDT's do emit several forms of radiation. We have become ultraconservative in the use of x-rays, especially during pregnancy. Should we not now have VDT operators wear lead aprons?

Even more frightening is a story published in a recent issue of the *Smithsonian* entitlcd "When Criminals Turn to Computers Is Anything Safe?" (*Smithsonian,* Aug 1982, p 117). In this fascinating article the author, Gina Kalata, tells how easy it is for anyone with a minimum of computer know-how to do a little "data diddling," or by using a technique called "super-zapping" to be able to extract all manner of information from a computer bank. She quotes Kcn Thompson of the Bell Laboratories of New Jersey: "Computers are marvelous. You can talk a computer into spilling its guts to you. You can steal forever and the person you steal from won't ever know that something is missing." A reporter, dressed as a repairman, simply walked into the computer room of a big corporation and by plugging into a computer he could obtain all the programmed information he desired. All he needed to do, hc said, was to ask thc computer for the entire list of passwords, and instantly the black box gave him a complete print-out.

Could this mean the end of the protection of the confidentiality of our patients' records? What is to prevcnt a "super-zapper" from punching keys to find out who has what—an abortion, a divorce, a bout with VD—enabling him to rattle a skeleton in a family closet?

This unhappy side of the computer picture gives pause to all of us in the medical profession. Obviously the matter of cathode radiation cannot be ignored with 500,000 home computers now in place, and many more in business and industry. But of greater concern is the potential for meddling with medical information stored in computer banks.

Could it be that the wizardry of computerized "high tech" as it insinuates itself into our modern society is, as Karl Marx put it years before the silicon chip made its appearance, "Like the sorcerer who is no longer able to control the powers of the nether world whom he called up by his spell"?[1]

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Special Editor for Idaho

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A Distinction in Terminology

To the Editor: In reading the August 1982 issue I thoroughly enjoyed the Information article entitled "The Bedside Sherlock Holmes,"[1] which I found directly relevant to my area of specialty practice. However, the article does contain a common misconception, which I and my fellow practitioners would like to see editorially corrected forevermore.

The opening sentence of the article refers to an "emergency room physician." I might note that this is a designation whose time has come and gone. Those of us who practice the newly recognized specialty of emergency medicine refer to ourselves, with pride and justification, as "emergency physicians"; it is our belief that this more accurately reflects the tremendous changes that have taken place in our field over the past several years. Although this terminology distinction may appear insignificant, I believe it captures the expectation of both our patients and our medical colleagues.

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Kicking the Habit: Benefits and Methods of Quitting Cigarette Smoking

STEVEN R. CUMMINGS, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems (such as dizziness, pruritus, insomnia, shoulder pain and urinary tract infections) encountered in primary care practice that generally do not fall into well-defined subspecialty areas and are rarely discussed thoroughly in medical school, house staff training, textbooks and journals. Often the pathophysiology is poorly understood and clinical trials to assess the effectiveness of diagnostic tests or therapies may be lacking. Nevertheless, these problems confront practitioners with practical management questions.

The articles in this series discuss new tests and therapies and suggest reasonable approaches even when definitive studies are not available. Each article has several general references for suggested further reading. We hope this new series will be of interest and we welcome comments, criticisms and suggestions.

—BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

CIGARETTE SMOKING is the most important preventable cause of disease and death in the United States. An estimated 325,000 people die prematurely in the United States each year because of cigarette smoking, and life expectancies of middle-aged two-pack-a-day smokers are eight years shorter than for nonsmokers.

This article will review a few of the most important links between smoking and specific diseases and review ways of helping smokers quit.

From the Division of General Internal Medicine, Department of Medicine, University of California, San Francisco.

Supported by the Kaiser Foundation Fellowship in General and Internal Medicine.

Reprint requests to: Steven R. Cummings, MD, Division of General Internal Medicine, 400 Parnassus Avenue, Room A-405, University of California, San Francisco, San Francisco, CA 94143.

Smoking-Related Disorders

Coronary Heart Disease

Approximately 25 percent of all deaths from coronary heart disease in the United States each year are attributable to cigarette smoking, and most of these deaths are sudden. For those younger than 65 years, smokers who quit smoking substantially reduce the risk of death from this disease even within the first year after quitting, though it requires 10 to 15 years for the risk to

decline to that of nonsmokers. After myocardial infarction those who quit smoking have 20 percent to 50 percent lower mortality during the next three to five years than those who continue to smoke.

Respiratory Diseases

Cigarette smokers lose 42 percent more work days than nonsmokers, mostly due to more frequent respiratory illnesses. Smokers are predisposed not only to frequent, severe and long-lasting upper respiratory tract infections, but also to bronchitis and emphysema.

For smokers in whom chronic obstructive lung disease has already developed, quitting smoking generally reduces cough and sputum production, and may improve forced expiratory volumes in a few. Those who continue to smoke lose airway function more rapidly than those who quit.

Cancer

An estimated 110,000 people in the United States will die of lung cancer in 1982 and about 85 percent of these deaths will be attributable to cigarette smoking. Lung cancer is projected to surpass breast cancer as the leading cause of cancer death among women during the 1980's.

Smokers are also 12 to 16 times more likely to have oral and laryngeal cancer develop and 2 to 6 times more likely to have esophageal cancer occur than nonsmokers. These risks are as great for pipe and cigar smokers as for cigarette smokers. The risk of cancer in those who quit gradually returns to that of nonsmokers during 10 to 15 years.

Population studies have also found a significantly increased risk of bladder, renal and pancreatic cancer among smokers.

Peptic Ulcer

Duodenal and gastric ulcers occur 1.5 to 2.0 times more frequently among smokers than among nonsmokers. In addition, peptic ulcers are only half as likely to heal as in nonsmokers during six weeks of intensive antacid or cimetidine therapy. Thus, quitting smoking may be as important to ulcer treatment as medication.

Pregnancy and Infant Health

Maternal smoking increases the risks of abruptio placentae, placenta previa, spontaneous abortion, neonatal death and sudden infant death. Infants born to smokers weigh an average of 200 grams less than those born to nonsmokers. Quitting smoking early in pregnancy reduces the risk of low birth weight to that of nonsmokers, and may reduce the risk of other complications.

The "Less Harmful" Cigarette

Over the past decade, the tar and nicotine content of the average cigarette in the United States declined 32 percent and 36 percent, respectively, and the proportion of smokers using filtered brands rose from 1 percent in the 1950's to 92 percent in 1979. The health implications of these changes are not clear. The tar and nicotine content of a cigarette as measured by automatic machine burning of cigarettes does not accurately measure the amount of tar and nicotine that is inhaled by the smoker. Smokers compensate for lower nicotine content in cigarettes by inhaling more. This may increase the inhalation of carbon monoxide and other toxins.

Long-term users of filtered and low-tar, low-nicotine cigarettes have a 10 percent to 40 percent lower risk of lung cancer than those who smoke unfiltered, high-tar cigarettes, but there is conflicting evidence about whether filter cigarettes lower in tar and nicotine reduce the risk of coronary heart disease. There is no evidence that filtered, low-tar and -nicotine cigarettes reduce the risk of respiratory disease, peptic ulcer disease, or the adverse effects on pregnancy. Smokers of these "less harmful" cigarettes remain at much greater risk of cardiac, pulmonary, malignant, and reproductive mortality and morbidity than nonsmokers and those who have quit.

Quitting Smoking

An estimated 29 million smokers have quit since 1964, but 30 percent of women and 40 percent of men still smoke. About two thirds of these current smokers have tried to quit at least once.

Nicotine Addiction

Most smokers are addicted to nicotine. This may explain why smoking is often so difficult to quit. During experimental intravenous administration of nicotine, smokers reduce both the number of cigarettes they smoke and the volume of smoke they inhale with each puff. When given experimental cigarettes of varying nicotine content, smokers tend to smoke more cigarettes and inhale larger puffs when the nicotine content is low than when it is high. These findings suggest

that smokers smoke in order to maintain a relatively steady serum nicotine level or at least to prevent nicotine withdrawal.

While attractive in its simplicity, nicotine addiction does not completely explain smoking behavior. When given nicotine-free cigarettes, most smokers will complain that the cigarettes are less satisfying but will continue to smoke. Moreover, about 10 percent of smokers experience no withdrawal symptoms after quitting. Therefore, it seems likely that social and environmental cues and pressures also play a role in sustaining smoking.

Withdrawal Symptoms

Withdrawal symptoms are the major reason that smokers fail in their attempts to quit. Some 90 percent of smokers report a variety of symptoms after quitting including craving for cigarettes, irritability, headache, insomnia, drowsiness, constipation, diarrhea and increased appetite. These symptoms are more intense during the first few days after quitting, and usually resolve within four weeks. However, some ex-smokers report craving for cigarettes years after quitting.

About two thirds of those who quit gain weight, averaging about 5 pounds. Although this weight gain is popularly attributed to an increased appetite, it may also be due to the decreased resting metabolic rate that accompanies withdrawal from cigarettes.

Methods of Quitting

About 95 percent of ex-smokers have quit without professional help. Health concerns are the predominant reason they give for stopping. Generally, smokers are more likely to quit because of current symptoms such as cough, dyspnea or sore throat than because of fear of future cancer or heart disease. Recent occurrence of a smoking-related disease in a friend or relative is also a common motive for quitting. The cost of cigarettes ($330 per year for one pack a day) is a reason adolescents often give for quitting, but cost rarely motivates adults to stop.

A wide variety of methods to help smokers quit have been developed, and all seem to have a similar pattern of efficacy. Each method initially helps 40 percent to 80 percent of smokers to quit, but most of these will relapse. Only 15 percent to 25 percent remain abstinent for one year. No single treatment method has proved consistently superior to others.

Aversive conditioning involves pairing a noxious stimulus such as an electric shock or a nauseating image with smoking. Most smokers who complete such treatments quit smoking and as many as two thirds of these may remain abstinent for at least a year. However, as many as half of the selected volunteers who start shock therapy drop out before the treatments are completed.

Rapid smoking is a form of aversive conditioning in which, over several sessions, smokers are asked to smoke cigarettes at a rate of about one puff every six seconds until they are unable to inhale another puff. It was initially claimed that by this method 100 percent of smokers quit and 60 percent remained abstinent at six months. However, recent studies of rapid smoking have found long-term abstinence rates of only 20 percent to 30 percent. During rapid smoking, carbon monoxide levels may reach 10 percent to 17 percent saturation accompanied by respiratory alkalosis. Because this combination may impair myocardial and tissues oxygenation, rapid smoking techniques are not recommended for smokers with significant heart or lung disease.

Stimulus control techniques involve systematic identification and avoidance of the social and environmental cues that the smoker associates with smoking. The smoker first records the situation in which each cigarette is smoked and then these situations are avoided, or modified. For example, a person who smokes during coffee breaks may substitute a brisk walk for his usual break or spend coffee breaks only in areas where smoking is prohibited. Because stimulus control techniques are so diverse, there has been no overall study of their efficacy.

Contingency contracting involves a contract by the smoker to quit and remain abstinent. The smoker may deposit money that is lost if he fails to quit or if he relapses. Contracts are probably more effective if they are made with nonsmokers.

Several techniques for reducing the severity of craving and other symptoms have been advocated including *hypnosis, relaxation training, biofeedback* and *acupuncture.*

Sedatives and other psychotropic agents have proved to be no more effective than placebos in helping smokers quit. Nicotine chewing gum has been used for several years in Europe and is undergoing clinical trials in the United States. The long-term toxicity of nicotine gum and its role in

helping smokers quit or ameliorating withdrawal symptoms is unclear.

Commercial Smoking Cessation Programs

Very few commercial programs have been critically evaluated. Those programs that use a multifactorial approach achieve higher success rates than those using a single method, but no optimum combination has been identified.

Follow-up is often neglected in commercial programs. If they provide follow-up at all, it is usually limited to voluntary reunion meetings or one-shot "booster" treatments.

Costs of commercial programs vary from no-fee or low-fee programs, sponsored by the American Cancer Society, the Lung Association or universities, to very expensive programs offered by for-profit organizations. For smokers who have smoking-related diseases or symptoms, some insurance policies cover certain stop-smoking programs. Information about local stop-smoking programs is available from local offices of the American Cancer Society and the Lung Association.

Physicians' Advice to Stop Smoking

While only 20 percent to 30 percent of smokers express any interest in commercial smoking cessation programs, 70 percent claim that they would quit if a physician gave them unequivocal advice to do so.

When physicians give advice to quit to patients who have no smoking-related symptoms, 5 percent to 20 percent will have quit by one year. On the other hand, physicians' advice to quit is generally more effective in those who have developed smoking-related symptoms and diseases. For example, in one study of smokers who had had myocardial infarctions, 63 percent of those who received a "special antismoking intervention" quit and remained abstinent for at least one year compared with only 27 percent of those who received routine care. The intervention consisted of dogmatic advice from a physician that the patient should never smoke and that quitting would reduce the risk of future myocardial infarctions. Similar advice was given to the patient's family, the patient was given antismoking literature and followed up periodically in an antismoking clinic.

Since smoking-related symptoms or diseases often motivate patients to stop, the occurrence of these symptoms or diseases provides the physician an opportunity for effective antismoking advice. Furthermore, because of the morbidity and mortality caused by cigarettes, even a small chance of success with any smoker is worth the effort.

TABLE 1

SMOKING CESSATION SUGGESTIONS FOR PHYSICIANS

1. If you smoke, set the example: quit.
2. Make advice firm and unequivocal.
3. Emphasize the health, aesthetic and economic benefits of quitting.
4. Follow up, especially during the first few months.
5. Give pamphlets and written tips on quitting (available from local offices of the American Cancer Society and the Lung Association).

SMOKING CESSATION SUGGESTIONS FOR PATIENTS

1. Set a date to quit.
2. Make a list of places and circumstances associated with smoking and make plans to avoid them.
3. Get rid of tobacco products and paraphernalia.
4. Make a contract with someone for quitting, and plan rewards for yourself when you succeed.
5. Try to quit "cold turkey." Reduce to 10 to 15 cigarettes a day as a prelude to completely quitting.
6. Remember that withdrawal symptoms will be transient.
7. Exercise may minimize the craving for cigarettes and the weight gain of withdrawal.
8. Spend more time with non-smoking friends and associates and minimize your contact with smokers.

Advice to quit should be unequivocal and should emphasize the functional, aesthetic and economic benefits of quitting. Physicians and other health professionals might also encourage nonsmoking by setting an example and by discouraging smoking in offices and workplaces.

A few smokers quit almost effortlessly but for most it is a difficult task that requires preparation and persistence. In general, smokers should set a date to quit. Before that day arrives, they can prepare in several ways. For several days they can record the number of cigarettes smoked and the situations in which they were smoked. They can then plan to avoid or change these situations during withdrawal. A recent or potential quitter should plan to spend more time with friends and associates who do not smoke and less time with those who do. They may also find it helpful to get rid of all tobacco products, ashtrays and lighters. Some may find that making a contract with themselves, or with nonsmoking friends, can provide extra determination to quit.

A physician can help by advising potential

quitters that withdrawal symptoms will be transient. Some patients may be able to minimize withdrawal symptoms, especially the craving for cigarettes, by physical exercise or simple relaxation exercises.

There is some evidence that quitting "cold turkey" may produce less discomfort than slow withdrawal. For those who cannot quit abruptly, progressive reduction of cigarettes smoked each day or switching to a very low-nicotine brand can be tried. However, most smokers find it difficult to reduce their cigarette consumption below ten cigarettes per day, so these reductions should be used only as a prelude to complete quitting.

Most ex-smokers relapse and most relapses happen during the first few months after quitting. This is a time when follow-up visits or phone contacts with a physician will be most effective in helping an ex-smoker achieve permanent abstinence.

An outline for quit-smoking advice is provided in Table 1. A wide variety of pamphlets describing benefits and methods of quitting are available from local offices of the American Cancer Society or the Lung Association.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Methylethylketone Damage of the Immune System

QUESTION:

Does methylethylketone damage the immune system?

OPINION:

It is the opinion of the Advisory Panels on Allergy, Internal Medicine, Pediatrics, Preventive Medicine and Public Health, and the Committee on Environmental Health that there is no scientific evidence that methylethylketone (MEK) causes damages to the immune system.

Refer to: McConnell TS, Cushing AH, Bankhurst AD, et al: Physician behavior modification using claims data: Tetracycline for upper respiratory infection (Health Care Delivery). West J Med 1982 Nov; 137:448-450

Physician Behavior Modification Using Claims Data: Tetracycline for Upper Respiratory Infection

THOMAS S. McCONNELL, MD; ALICE H. CUSHING, MD; ARTHUR D. BANKHURST, MD; JAMES L. HEALY, MA; PATRICIA A. McILVENNA, MA, *and* BETTY J. SKIPPER, PhD, *Albuquerque*

Professional Standards Review Organization claims data were used in defining, planning, implementing and evaluating an approach to an ambulatory medical care problem utilizing educational intervention. Modification of physicians' tetracycline prescribing behavior was achieved in an actual practice setting by personal visits from peer physicians.

FEW SUCCESSFUL physician behavior modification strategies have been described for ambulatory care using claims based data.[1,2]

The New Mexico Professional Standards Review Organization (NMPSRO) Ambulatory Care Demonstration Project was funded to test the limits to which claims-based data could support professional review, to utilize data being collected as a part of the Medicaid Management Information System, and to study three specific areas, of which behavior modification of provider practices was one.[3] The goal of the Behavior Modification Project was to determine whether providers of ambulatory medical care could be influenced to change their diagnostic or therapeutic habits through personalized educational intervention. The following describes the planning, implementation and evaluation of one such effort.

From the New Mexico Professional Standards Review Organization, Ambulatory Care Demonstration Project, Albuquerque.

Supported by DHEW Contract HSA-024-750003, Modification Eleven.

Reprint requests to: Thomas S. McConnell, MD, University of New Mexico Hospital, 2211 Lomas NE, Albuquerque, NM 87106.

Methods

More than 15,000 tetracycline prescriptions were billed to the New Mexico Medicaid Program in 1976, making the drug one of the most frequently prescribed antibiotics in the program. Between January 1976 and June 1977, a total of 156 providers prescribed tetracycline 1,584 times for 1,346 ambulatory patients for diagnoses of upper respiratory infection, including viral upper respiratory infection, streptococcal pharyngitis, acute tonsillitis or acute pharyngitis.

The use of tetracycline for the above diagnoses was considered to be inappropriate by physician members of the PSRO.[4-6] Based on scientific merit, frequency and data identifiable from claims, this problem was chosen for a real-time behavior modification study. The 35 physicians most frequently prescribing tetracycline in ambulatory cases of upper respiratory infection as defined above were selected for the experimental and control groups.

These 35 physicians, constituting 22 percent

of the practice pool, wrote 975 (or 62 percent) of the tetracycline prescriptions for 801 patients.

Four variables—MD versus DO, urban versus rural, board certification versus none and prior NMPSRO contact versus no NMPSRO contact—were used in dividing the physician providers into four strata which were made as homogeneous as possible. Then the experimental and control physicians were selected randomly from each stratum. In this manner, 18 physicians were placed in the experimental group and 17 in the control group. The study group was reduced to 33 physicians when one control group physician was found to have died and another provider refused to be visited when contacted as a member of the experimental group. This left 17 physicians in the experimental group and 16 in the control group.

As a result of matching and random assignment to group, the average previsit prescription rate was higher in the experimental than in the control group. Therefore when evaluating the postvisit intervention effect, analysis of covariance was utilized with the previsit prescription rate as the covariate. The intervention for experimental group providers was to be a personal visit by a PSRO physician member; control providers were to receive no personal visit or other contact by PSRO.

Five physician consultants carried out the personal visits; two pediatricians, two internists and one family physician. Appointments were made personally on the telephone by the visitors, requesting 30 minutes time at the convenience of the physician to be visited. All of those participating as visitors took part in visit rehearsals to insure consistency. Visits were to be as nonthreatening as possible, maintaining an "educational" tone and presenting both claims data gathered for the physician in question and educational materials.[4-6] The message of the visit was to be that tetracycline was not the drug of choice for streptococcal infections, and not indicated in cases of viral upper respiratory infection.

The five physician consultants made visits to the providers, located throughout New Mexico, during six weeks in the winter of 1977-1978.

Results

In the six-month follow-up period, eight of 17 providers from the experimental group continued to prescribe tetracycline for upper respiratory infections while 15 of 16 control providers did so (see Table 1). This difference between the two provider groups is statistically significant (Fisher's exact test, $P<.01$). The mean number of prescriptions written by both experimental and control physician groups decreased significantly in the follow-up interval as compared with the preintervention period (experimental group, Wilcoxon signed rank test, $t=149.5$; $P<.001$; control, $t=117.5$; $P<.001$). However, analysis of covariance showed that the reduction in the mean number of prescriptions in the experimental group was significantly greater than that of the control ($F=4.34$, $P<.05$).

TABLE 1.—*Prescriptions of Tetracycline for Upper Respiratory Infections: Experimental Versus Control Providers*

Experimental Group Provider	*Prescriptions Before Visit Period 6-Month Average**	*Prescriptions After Visit Period 6 Months*	*Control Group Provider*	*Prescriptions Before Visit Period 6-Month Average**	*Prescriptions After Visit Period 6 Months*
E1	33.0	4†	C1	4.0	0
E2	33.0	0	C2	4.0	4
E3	26.5	1	C3	2.5	4
E4	24.0	0	C4	5.5	4
E5	21.0	9	C5	4.5	2
E6	13.0	1	C6	3.0	2
E7	10.0	1	C7	10.0	2
E8	6.0	0	C8	7.0	2
E9	6.0	3	C9	11.5	5
E10	6.5	10	C10	4.0	2
E11	8.0	0	C11	9.5	5
E12	6.0	1	C12	8.5	2
E13	2.5	0	C13	16.0	7
E14	5.5	0	C14	9.5	2
E15	4.5	0	C15	18.0	7
E16	3.5	0	C16	4.0	2
E17	4.5	0†			
Average Per Provider	12.6	1.8	Average Per Provider	7.6	3.2

*Two 6-month Jan-June periods (1976 and 1977) before the visits were averaged.
†These two entries represent only 5.5 months of data because the visits took place in mid-January 1978.

Discussion

A statewide PSRO was able to alter significantly for the better a scientifically sound medical problem by an educational intervention in which practicing physicians met with other practicing physicians. Personal visits had a positive impact on the prescribing habits of these providers.

Contamination of the control group ("word got around") could account for the reduction in the mean prescription rate in that group. Such change may not simply be a spurious study phenomenon. It may represent an analog to the placebo effect, one in which blinding is not successfully maintained. Or, it could be an indication

that mere communication of information to physicians, however informal, is sufficient to induce the desired effect. If true, then the effect of the intervention would be even stronger than that measured by this study.

A possible bias exists in having the top five providers in the experimental group. This, however, was believed to be statistically more tolerable than the bias which would have been introduced by having most MD's in one group and most DO's in the other, or most rural providers in one group and most urban in the other. By the use of covariant analysis, such bias has been minimized.

The goals of the project were achieved: the claims-based data system was used to define a problem of medical care delivery to the Medicaid population, an intervention method was planned, implemented and evaluated. The more basic problems of inappropriate use of antibiotics for nonbacterial respiratory infections, failure to obtain cultures to detect group A β-hemolytic streptococcal disease and interpretation of cultures of normal pharyngeal flora were not addressed.

This study shows that, at least in the short term, modification of physicians' prescribing habits is possible in an actual practice setting.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Reconsideration of Repository Emulsion Therapy

QUESTION:

Is repository emulsion therapy in the treatment of allergy conditions considered accepted medical practice? If so, for which conditions and under which circumstances?

OPINION:

It is the opinion of the Advisory Panel on Allergy that repository emulsion therapy is not considered accepted treatment for allergy conditions.

Refer to: Minkowski WL: Medical adventure in South America (Medicine in Perspective). West J Med 1982 Oct; 137: 451-459

Medical Adventure in South America

WILLIAM L. MINKOWSKI, MD, MPH, *Los Angeles*

During a six week period in the summer of 1981 I rediscovered the rich personal and professional rewards of sharing medical skills with those in need. An odyssey that began with a volunteer assignment in a Catholic mission hospital in Georgetown, Guyana, continued by sheer chance on the streets of La Paz, Bolivia, and aboard an antiquated train en route to the Inca capital of Cuzco, Peru.

Guyana, an Amerindian word meaning *land of many waters,* aptly describes a tropical country quadrisected by three major rivers and bordered on its north coast by 270 miles of South Atlantic Ocean (Figure 1). Granted independence by Great Britain in 1966, Guyana has been cast in the role of a Second World nation,* neither impoverished of natural resources nor yet fully capable of managing its own affairs. Misguided economic policies have brought this fledgling Caribbean country close to disaster, propelling substantial numbers of professionals and technicians into flight to more stable and prosperous areas of the western world. The exodus of physicians has left Guyana with an enormous deficit in competent medical personnel and services, a circumstance that prompted the St. Joseph Mercy Hospital to seek outside help.

The population of Guyana is comprised of two major groups, East Indians (53 percent) and blacks (32 percent). About 11 percent are mixed. The blacks were brought from Africa as slaves to work the plantations of European masters. When they were liberated in the early 19th century, overpopulated India provided their replacements. Thousands of its citizens were indentured with the lure of work and ultimate economic independence. The only native group, the Amerindians, whose Asian origins are thought by local anthropologists to be shared with North American Indians, rejected in turn the civilizing influences of the Dutch, French and English colonists, retreating to the interior forests and savannahs to pursue more traditional sedentary and nomadic existences. Much smaller numbers of Portuguese and Chinese make up the remainder of Guyana's permanent population.

Georgetown, capital of Guyana, has a population of less than 200,000. The vestiges of its once handsome exterior remain in its lovely wood homes, stilted for protection against the wet season floods and to exploit trade winds blowing inland as mitigators of an otherwise enervating equatorial climate (Figure 2). Tropical plants, often fragrant and brightly colored, are irrepressibly luxuriant. Boulevard grasses are neatly cropped by nomadic cows, horses and goats, freely roaming the city's streets. The entire city is traversed by an empoldering system of irrigation and drainage canals (Figure 3) introduced by the early Dutch settlers. Beyond flood control regulated by *Kokers,* the Dutch word for sluice gates, these canals add a decorative touch to the flat, coastal plain. Transportation is provided by buses, shared taxis and private autos, all operating erratically as imported replacement parts become ever scarcer and more costly. It is the marketplace, however, that stimulates the senses and reveals the vitality of the city. Every ethnic group and social class walk its refuse-carpeted paths,

*I am defining Second World countries as those neither industrially developed in the American/European/Japanese sense nor impoverished or underdeveloped as are nations in Central America, Africa and Asia.

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accepting the risks of jostling, slipping and the nimble fingers of pickpockets. The sounds of hawking vendors carry the message of food for the table in English, Hindi, Urdu and a variety of regional dialects. Sacks and baskets arriving empty leave the market overflowing with home-grown edibles.

The distribution of health care services in urban Guyana differs little from that in First World countries. The affluent make exclusive use of the few remaining private practitioners and private hospitals. Unskilled and skilled workers, insured through company or government programs, use both private and public facilities, the choice dictated both by convenience and the practice habits of physicians. The indigent have no alternative to the public clinics. The St. Joseph Mercy Hospital (Figure 4) has 120 medical and surgical beds. Its widely accepted reputation for cleanliness and for providing the best health care in the country may not be undeserved. Indeed, many of its patients come from long distances, deliberately

Figure 1.—The Northeast Coast of South America.

Figure 2.—Houses built on stone pillars in Georgetown for protection against flooding.

avoiding government and other private hospitals within easier reach. I saw many sick patients wearied by a four-hour bus ride from distant villages. My daily assignment was the outpatient service, shared with one internist and one generalist, both East Indian, trained in the British Isles. Sister Mary Liguori, a certified, American-trained surgeon, is the hospital's only full-time, permanent physician. One obstetrician, one ophthalmologist and one otolaryngologist, all part-time employees, compose the remainder of the medical staff.

The conditions under which I worked were far less spartan than those I knew in rural West Africa,[1] yet inadequate by western standards. I had a small desk whose surface was papered with a large selection of insurance, prescription and sick-leave forms, each serving different health care programs. The need for the latter forms quickly became apparent when almost every adult I saw requested at least three days of paid leave, a request that bore no relationship to the illness. The examining table was a hard bench

Figure 3.—One of the empoldering canals in Georgetown.

Figure 4.—St. Joseph Mercy Hospital.

without stirrups. Illumination for all orifices had its source in a standard pocket penlight whose batteries generated an ever alternating current. A single sheet covered the table, scented and soiled by the warm bodies of 20 or more patients examined in each morning and afternoon session. There were neither gowns nor drapes. The needle of a wall-mounted sphygmomanometer rested disconcertingly far from zero. One otoscope was available whose vintage would be prized in any museum display of ancient medical instruments. A single stainless steel speculum, washed with soap and water after each use, served all women. A few shortened, roughly planed tongue blades completed the inventory of my working equipment. A noisy, rotating fan attached to the wall left me alternately windblown or uncomfortably warm and invariably straining to hear the spoken word.

Those tropical parasites with alien names that had become so familiar to me in rural Africa were comparatively rare in Georgetown. Only small foci of endemic malaria survive along the coastal zone. *Culex* and *Aedes* mosquitoes, hosts of *Wuchereria bancrofti,* are abundant. Filariasis in its acute and chronic forms is a common outpatient diagnosis, usually confirmable by identifying microfilariae in a 10 PM specimen of blood. This nematode, together with an occasional case of ascariasis and enterobiasis, were my essential links with tropical medicine. Leprosy is endemic in Guyana. Most cases are managed by an English dermatologist at the National Hospital in Georgetown. I saw one male leper with old, extensive tissue loss of digits and nose and referred for biopsy three young adults with skin pigment and neurologic changes that are the early heralds of leprosy. However, the most common illnesses of urban Guyanese are not different from those seen in the United States: obesity, respiratory infections, allergies, hypertension (among all races), diabetes, gastrointestinal dysfunctions, trauma, urinary tract infections and the sexually transmitted diseases, among others. In a similar equatorial climate in far more primitive areas of West Africa with its legion of parasitic pathogens, I had observed that most of the diseases common to temperate and subtropical United States are also widespread there.

It was neither the absence of modern medicine's computerized diagnostic gadgetry nor the age of available equipment that posed the major obstacle to offering care of good quality. In the bowel dysfunctions seen so frequently in older patients, for example, stools negative for occult blood only fleetingly assuage concerns for an underlying neoplasm. Grievously missed were a sigmoidoscope and a radiologist to direct the filming and offer interpretations of barium studies done by a technician. Films were always of inconstant quality. Their readings devolved upon the referring physicians, none of us trained in diagnostic radiology. The hospital laboratory is adequate for the common problems in hematology and bacteriology, less so for chemical analyses. Thus, its enzyme determinations include only amylase and SGOT, a limitation which, with the unpredictable availability of a technologist after 5 PM, I found restricting in managing the frequently presenting complaint of chest pain. In addition, the laboratory is unable to titer the VDRL or to do a specific treponemal test for syphilis or a culture for the gonococcus. In an urban community with few rigid constraints on sexual behavior, frequent epidemiologic treatment for these venereally transmitted infections was unavoidable. This concept of preventive therapy appeared to be unfamiliar to the local practitioners of medicine.

The Mercy Hospital has a single operating room shared five days a week among two general surgeons and the two part-time specialists. For general emergencies occurring during hours assigned to the latter surgeons accommodation is possible but disruptive of schedules and of feelings. Resolution of that dilemma often required transfer of a patient to another hospital. The one constant lament of all of us was the chronic lack of essential supplies. Shortages included dressings, parenteral fluids, antibiotics and a host of other medications. There is no blood bank in Guyana. Families are expected to provide needed blood on call. Of greater concern to me in the outpatient section were the always inadequate quantities and erratic availability of drugs with specific pharmacologic utilities. Aqueous procaine penicillin had not been seen for a year. On an almost daily basis my calls or visits to the pharmacy uncovered very roughly equivalent substitutions for my prescriptions among a haphazard assortment of American, French and British products. While the essential ingredient may be identical, brands differed in concentrations and unwanted chemicals were often incorporated into a single preparation. No less distressing was the discovery that many items dispensed daily were outdated by many months, a practice understandably born of necessity but al-

ways raising the question of loss of potency. In truth, there are no alternatives in Guyana. All drugs are ordered by a central government agency whose sense of urgency seems to bear little relationship to the needs of health care providers. On occasion a timely gift from the United States or Europe helped to maintain some essential service, persuading the Sisters of Mercy of the efficacy of their prayers.

Having heard so often the refrain, "I don't want to go back to the government hospital," I needed but a single visit to the mammoth national hospital in the capital to understand the reluctance of many Guyanese to make use of its services. Its wood buildings have suffered the inexorable decay of time and humidity and the almost irremediable insult of neglect. There is little here to invite the sick through its portals. For the courageous or the desperate, entry is less than reassuring for inside walls and floors are no more attractive than its exterior surfaces. On all wards beds are packed tightly, allowing little room for passage much less for elementary privacy. On the orthopedic floor multiple casted limbs in a single bed testified to the double occupancy policy dictacted by demand. I observed the same bed-sharing among gynecologic patients. However, on my one visit to this hospital I was not privy to the ultimate in inpatient intimacy, three bodies in a standard hospital bed. This not so rare occurrence was reported to me by my official nurse guide. With admirable, if reluctant honesty, she admitted that drugs and supplies are often not provided for patients and that the inconstancy of replenishment of all medical items plagues this largest Guyanese hospital no less than the private institutions. A hasty review of several randomly selected medical charts showed (1) the absence of historical and system review data, (2) a paucity of daily rounds notes by physicians and (3) heavy prescriptive ordering of "symptomatic" medications compounded of multiple ingredients. While nurses were present in appropriate numbers, doctors were scarce among several wards, each with dozens of beds. Breakdowns in equipment, unrepaired for long intervals, are frequent. Raised on pillars that support all buildings in Georgetown, the underbelly of piping is obscenely exposed. The drip of fluid leaks left their small ponds on dirt or concrete surfaces, with scattered rivulets sinuously seeking the network of drainage ditches coursing through the grounds. As we walked among the buildings, an occasional foul stench suggested that excretory sewage was not always fully contained.

Nurses trained by the government are required to serve in national hospitals for several years. Those graduating from St. Joseph Mercy Hospital are free to choose among any of the nation's health care facilities. Recently passed legislation, however, compels all nurses to give some service to a government health facility. I had not been in Guyana long before I was deluged with requests by nurses for information about working conditions and opportunities in the United States. Are nurses needed? Do many of them specialize? What are the choices for an inexperienced nurse? How much do nurses earn? Do their incomes support a comfortable life-style? The economic basis for these inquiries was quickly apparent. Only a few years ago 40 percent of all Guyanese earned less than $G300 yearly and only 10 percent had annual incomes exceeding $G500. At that time the US dollar was worth about two local dollars. Today the exchange rate is three to one. Nurses in private hospitals with 15 or more years of experience earn the equivalent of about $150 (US) per month. The incomes of private practitioners of medicine were never revealed to me. Their homes and life-styles suggested few privations. Physicians employed by the state manage a comparatively comfortable existence but with few opportunities for travel either for professional or recreational purposes. Mercy Hospital offers its contract physicians from abroad a salary of about $700 per month, compensation only modestly improved by the provision of low rent housing.

There is no medical school in Guyana. Most of its black physicians have been trained in the West Indies or, more recently, in Cuba. East Indian doctors more often have attended schools in the British Isles or in Canada. The former are largely employed in government facilities, the latter in private practice. There is also an expatriate group invited by the Ministry of Health to ameliorate the shortage created by the flight of native physicians. These come primarily from the Philippines, Korea, India and Cuba. In Guyana's hospitals there are no organized departmental meetings that serve a teaching purpose. No professional committee exists within private hospitals charged with establishing, much less monitoring, standards of practice. The few hospital libraries I saw possess old texts and journals, the majority cast off by members of the staff. An exceedingly

tight national economy with rigid controls of foreign purchases discourages subscriptions to professional journals. In such an indolent academic climate it is not surprising that autopsies are almost never done. When done, the family of the deceased must provide the glass jars for tissue specimens. Limited and unreliable refrigeration does not aid the cause of postmortem examinations. At mortuary entries there is a removable sign that seemed in constant motion during my stay: "Refrigerator Out of Order. Please Take Body Elsewhere."

I had few professional contacts with the aboriginal population of Amerindians, of whom there are about 40,000 left. Only a handful live in the developed coastal zone. One 55-year-old man with chronic filarial lymphangitis of both legs and scrotum shared with me some of his early health experiences with a tribal shaman. Village healing is still widely practiced and accepted by the Amerindians insulated from urban centers. It is a skill compounded of experience that begins early in life with the teachings of an established practitioner. Encompassing an understanding, however unsophisticated, of the pharmacology of plant and animal substances, it also demands a large measure of faith. The medicine man is held in high esteem, functioning as a supernatural power able to overcome disease, fear and evil influences. For example, in Crawak villages the *semichichi* can perform the *jawuhu* ritual, blowing on pieces of broken bottle, thorns and poisonous materials, "sending" these into the body of his client's aggrieving enemy. However irrational to the westerner, the effects on the intended victim are unmistakable: organ dysfunction severe enough to disable and, at times, even death. Plants provide the most important sources of healing agents. Chewing nutmeg heals speech impairments. *Wiriwiri* peppers thoroughly cleanse the clogged colon. Creole women use calabash leaf for inducing abortion; their men drink *capadulla* bark tea for improving potency. For contraception a piece of ropey vine, *buyan,* remains effective so long as it rests under a woman's bed. Snake bites are treated with crushed worms applied to the puncture wound and also eaten. Lime juice for the common cold has its counterpart in the popular US use of ascorbic acid megatherapy. My informant admitted that before migrating to Georgetown from the interior, long experience with his village doctor had been both satisfying and revealing of his healing limitations.

As a short-term guest at Mercy Hospital I was ripe for exploitation as the visiting "professor." While I may have exposed the students to some fresh insights into a variety of community health problems, it was I who came away enriched by our classroom discussions. Alcoholism is epidemic in Guyana, its etiologic roots no less complex than in our own society. The nonalcohol drug scene deserves but a brief footnote in the playbill of the drama of drug abuse. Cannabis products, for example, are available but their use is limited. The hard drugs appear to be far more familiar to Guyanese by name than by use. In the area of marital relationships my observations that classical psychosomatic complaints were notably more frequent among married East Indian women than among blacks, led to some forthright comments about traditional Hindu inequalities between the sexes. In searching for explanations my questioning of patients elicited the reluctant admissions of

Figure 5.—Mt. Veronica, a 23,000-foot Andean peak in Peru.

marital discontent and frustration. Specific manifestations varied but the common cry was the gross disparity in rights between husband and wife. What emerged from the classroom talk with the young East Indian and black students, including one young man, was an acknowledgement of the frequency of repression of the wife by Indian husbands. Moreover, all of them agreed that for the woman escape from an intolerable marriage through divorce is almost impossible. Hindu orthodoxy compels permanent fidelity to a husband. Not even in death is there mitigation of a wife's expected loyalty to her spouse. Today, in urban centers in India and in Georgetown, four generations removed from indentured forebears, distance, time and exposures to other cultures have begun to sap the force of this and other centuries-old customs.

When I bade farewell to the Sisters of Mercy to begin my brief journey through the Andes, I had assumed that my professional involvements had ended until my return home, that only the serenity and stunning vistas of towering snow-laden mountains lay ahead (Figure 5). In the Indian marketplace of La Paz, Boliva, I discovered the *Mercado de los Brujos,* the Sorcerer's Market. It is physically separate from the vast sprawl of street vendors blanketing an old, hilly quarter of that highest of all world capitals. Curiosity, not my search for relief from a nagging headache generated by the rarefied atmosphere at 11,000 feet, led me to question the medicinal merchants about traditional Indian medical practices. The healing skills there are an intrafamilial male monopoly, passed through succeeding generations by word of mouth. Since I was not sworn to silence, I feel no sense of betrayal in sharing but two of their numerous diagnostic secrets that should endear American physicians to their time and cost conscious patients. In each case it is the prognosis that is revealed by the procedure. In the first the blood of a freshly killed rabbit is poured on the torso of the patient. By its color and odor changes this test rapidly and accurately establishes the gravity of an illness. For the squeamish there is an alternative approach to the same objective and much preferred for its widely heralded sensitivity. The healer places a fresh hen's egg in the patient's axilla, either left or right. Allowing 10 to 15 minutes for critical chemical reactions, he then requests that the egg be squeezed between arm and chest wall until the shell breaks. The darkness of its contents can be reliably correlated with the seriousness of disease. The objections I raised to these methods in the interest of a rare, overly fastidious person failed utterly to move my interviewee. The street patient, armed with an Indian healer's instructions, seeks out a trusted pharmacist whose impressive display of plant and animal products in an endless variety of colors, sizes and forms (Figure 6) covers a huge blanket laid out on a sidewalk or street. The medicinal vendor deals only in cash, the healer only in barter. His preferred currency is food. If his pre-

Figure 6.—Llama fetuses for sale by a medicinal vendor in the Sorcerer's Market of La Paz.

scriptive skills relieve distress, a gift consonant with symptomatic improvement is offered in addition.

Although La Paz has its own medical school and teaching hospital, Indians most often choose first to consult a traditional healer. This route to health care is culturally determined, not a rejection of modern medical practice. The one widely bruited complaint about the newer medical care system is that "the doctor always wants me to return for more tests," a lament not unknown in the United States. My interviewees made no allegations about the inferior quality of current medical teaching. What was clearly implicit in their comments was the feeling that the system fails its students when they cannot make accurate diagnoses in a single, brief visit.

Graduates of the national medical school are required to serve their country as physicians for one year. Rural Bolivia, very different from rural United States, attracts no permanent medical settlers. The lures of a house, a furnished clinic, a nurse and an ambulance, together with a monthly stipend of $150, engage few candidates. Brewing at the time of my visit there was a doctors' strike against the government's salary schedule. An acute problem in Bolivia is the plethora of physicians in the few major urban and suburban areas. Unemployed doctors in La Paz are not rare. This urban excess is undiminished by a 40 percent rate of specialization among young graduates who must find their advanced training programs abroad. Having done so, the majority discover foreign practice pastures to be far greener and often choose not to return home. Those who do still find their already surfeited cities irresistible.

Figure 7.—The setting for Machu Picchu (Old Mountain)—Inca religious center, fortress or both.

From Puno, Peru, on the north shore of enormous and exquisite Lake Titicaca, I began an 11-hour marathon by train across the Peruvian Altiplano (high plateau) to Cuzco, famed center of Incaic civilization. It is also the gateway to mystical Machu Picchu, an architectural gem in a natural setting of incomparable beauty (Figure 7). With the Peruvians I shared the ancient, noisy carriages pulled by one wheezing, coal-fired engine, the dirty, primitive toilets without paper or wash water, and the food prepared and served by unwashed hands.

I was not fated to make that journey without medical event. At a village two hours out of Puno a 27-year-old Indian woman entered my carriage. She had an infant shawled to her back, one 5- and one 6-year-old boy held in tandem with one hand and a heavy bundle of clothes carried in the other. She was no less impoverished than all rural Indians. Briefly, she told me that she was visiting her husband who had recently found work in Cuzco but was now in a hospital for an unknown disease. It was shortly after lunch when I noted that the 6-year-old boy's face was deeply flushed. His skin felt unmistakably fevered. I learned from his mother that he had complained of feeling cold the preceding night and had awakened that morning with pain in his left chest. That was the entire story. With mother's approval and without a Peruvian license to practice medicine I lifted the boy to the table. Between the din of the train and the babble of multilingual passengers, my age-impaired hearing caught the crackle of inspiratory rales at the left base. A profoundly grateful mother accepted my traveler's supply of ampicillin for her son and instructions for follow-up at

the hospital in Cuzco. She informed me that in her village there was neither a physician nor a nurse. Had she not been en route to the city, she said, she would not have consulted her village healer until convinced that the boy was really sick.

This experience in international medicine was very different from that in equatorial Africa. With fewer exotic parasites to challenge me in Guyana, many intimate interpersonal exposures offered more than compensating rewards. Though separated not only by the broad Atlantic Ocean but as well by language, race, customs and, indeed, by centuries of time, Africa and South America are joined by people who share the same, often desperate, need for modern health care. Therein lies the essential ingredient of a satisfying medical adventure.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Bone Densitometry

QUESTION:

Is bone densitometry an effective diagnostic tool?

OPINION:

It is the opinion of the Advisory Panels on Internal Medicine and Orthopedics that bone densitometry is an effective tool for measuring bone density and, therefore, is an accurate and sensitive means of following changes in density during the course of disease. It may be used as an adjunct to diagnostic procedures for osteoporosis and allied conditions. Because its use must be well controlled to be accurate and the equipment necessary for the procedure is moderately expensive, the indications for use should be documented.

Refer to: Schoolman HM: Anatomy, physiology and pathology of biomedical information. West J Med 1982 Nov; 137: 460-466

Anatomy, Physiology and Pathology of Biomedical Information

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INFORMATION PROCESSING is a fundamental function of clinicians. The purpose of this paper is to explore briefly the structure and function of biomedical information in relation to clinical problem solving. Unfortunately, very little is known about the structure of information and that lack of knowledge constitutes the major bottleneck to progress in information processing. As in other cases when fundamental knowledge is lacking, initial efforts are directed at characterizing and finding useful models. Although considerable progress has been made in characterizing and modeling the structure of information, efforts to arrive at an acceptable definition or to create a usable notation leave much to be desired.

Definition of Information

For biomedical information, we might adopt a functional definition that information is the useful organization of data. Such a definition makes it convenient to think of a datum as a unit—not of information but of the stuff of which information is made. One familiar way to characterize data is with regard to reliability. The concept of reliability contains two concepts, precision and accuracy. Precision describes the reproducibility of an observation while accuracy refers to how close it is to the "true" value. Contrary to our intuitive judgment, it is clear that for clinicians, precision is more useful than accuracy. To further explore the relationship of precision and accuracy, let us look at a situation where we expect very little variation.

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Figure 1 shows the published literature data on the thermal conductivity of copper that is 99.99 percent pure. The dark line does not represent actual data, all the other markings represent observations reported in the literature.

Clearly, if one were to build something in which the thermal conductivity of copper was important, his chances of choosing a value from the literature that is accurate are almost zero. Now, although the variation in 99.99 percent pure copper is orders of magnitude smaller than the variation in humans, it is not zero. Some very small part of this enormous variability is intrinsic to the differences between specimens of pure copper, but the vast majority is not.

If information is the useful organization of data, then how does one organize these data to make them useful? If one wished to adopt the view that all these observations were made with equal care, by equally good methods and by equally good observers, one could derive arithmetically a maximum likelihood solution from these data. However, the Center for Information and Numerical Data Analysis and Synthesis[1] chose to examine each datum and have it evaluated by experts for validity of method, care of observation, track record of investigators and, I suspect, some gut feeling. By this device they eliminated a fairly large number of points and from the remaining created the dark line shown in Figure 1. This represents their considered judgment as to which is the best value to use. While this line may indeed represent the best value to use if you are building something, it clearly is not the best line if you want to predict what value an investigator will get if he explores the question. In clinical medicine we do not usually build anything. Rather,

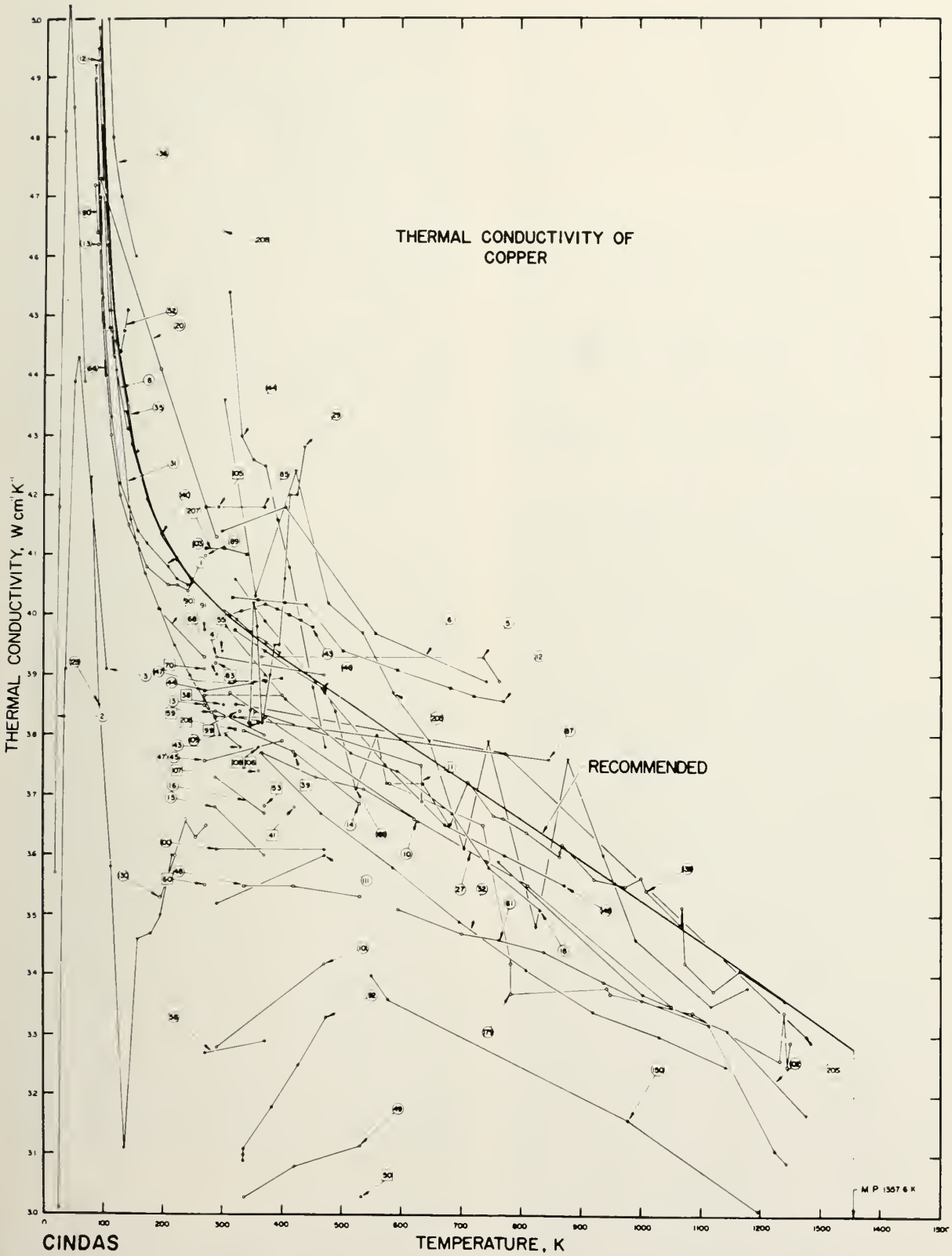

Figure 1.—Graph illustrating the published literature data on the thermal conductivity of copper.

we want to use the information to compare it with the same information on our patient, to help us predict how the patient will act, or to classify him with other previous patients. Since we are not building anything, it is not so important what the "true" value is. What is important is that every time the same conditions prevail, the same value is observed.

Characteristics of Biomedical Information

Because precision is more useful than accuracy, there is a strong tendency to rely on measurements that are known or thought to be precise. Perhaps it is more correct to say there is a strong tendency to downplay the importance of observations of questionable precision. Since many observations at the bedside require time, care and some degree of expertise to make, there is an enormous variation between observers, especially if those observers are chosen at random.

In general, observations made by machine are more reproducible than observations made by humans, thus the tendency to place more reliance on observations made by machines. This has contributed significantly to a much greater laboratory dominance over clinical observation than when I was trained. The implications of this are complex. Because the data are frequently quite different, the argument can be made that greater emphasis should be placed on clinical observation in order not to diminish the effectiveness of our clinical decision making by eliminating important information. But the argument can also be made that it is the clinical decision that is important, not the input or even the process that led to it. We should then seek the most effective and efficient means of clinical decision making. The observer variation among clinicians is too great to ever be efficient. The question deserves examination. The resolution should be clearly made in support of our underlying task, decision making, and not because of our emotional reactions to either bedside observations or machines. If clinicians recognize decision making as their fundamental task, then biomedical information might be defined as the organization of data in a manner that makes them useful in decision making.

In the field of viral hepatitis, 16,000 citations were retrieved from MEDLINE files covering a ten-year period. The retrieval was limited to English language citations, so clearly 16,000 is a significant underestimate of the number published in the world. Moreover, MEDLINE only indexes 3,000 serials out of the more than 20,000 received by the National Library of Medicine. I have no idea of the average number of data per publication and obviously these data were directed at more than a single question about viral hepatitis. How does one go about organizing these data in a useful way?

Dr. Lionel Bernstein and his colleagues at the National Library of Medicine created a synthesis of some 40 already existing analyses and syntheses done by experts in the form of review articles.[2] When they had finished, those references cited by the experts for statements that were included in the *hepatitis knowledge base* numbered 575. The hepatitis knowledge base was constructed in an hierarchical fashion. It consists of a general synthesis statement for each subject covered. This synthesis statement expresses the state of knowledge. The next level of the hierarchy consists of statements from the original review articles that form the basis of the general statement. Finally, references are given to the original work cited by the experts who prepared the review articles. Upon completion, ten experts concluded that it accurately reflected the state of knowledge at that time. Yet, only 575 citations were included from among the more than 16,000 available.

There are a number of possible interpretations of these data, all of which probably suggest characteristics of the biomedical literature:

1. There is an enormous redundancy in the published literature.
2. A great deal is published that for a variety of reasons is not considered useful. Parenthetically, one may note that 50 percent of the published literature is never cited in another publication.
3. Since there is so much of it, some has never been read, at least not by the experts.
4. That some of it has not been read appears to be of little importance, perhaps because of reasons one and two.
5. A significant portion of the data contradicts another significant portion of the data. This is especially true when considered over the period of a decade. "Facts" are very ephemeral in nature and concepts are not much more lasting.

Medical Education

With regard to facts and concepts, a paper written by Anderson and Graham from Kings College Medical School in London will be of particular interest to medical students.[3] Their

general thesis is that information overload is among the most pressing problems in education, and nowhere is it more clearly evident than in medical education. Without taking the time to detail either definitions or methods, let me simply state they estimated that during what they call the basic science curriculum, a student is called upon to assimilate 47,900 facts and 29,900 concepts that are indexed in standard textbooks for these subjects by 19,800 unique terms. Assuming 40 hours a week for 40 weeks a year, during two years a student is called upon to assimilate about 24 new facts or concepts per hour every hour.

A similar analysis for what the authors term the clinical part of the course, yields a need to assimilate 27,000 facts and 25,500 concepts which, on the assumption of a 40-hour week, 50-week year, is a learning rate of about nine facts or concepts per hour, every hour. In this estimate, no allowance has been made for the considerable time the student must spend acquiring practical skills and learning procedures.

By similar methods, they estimate that, for example, a student reading modern languages at the university would be asked to assimilate about six facts or concepts an hour. They further estimate that a reasonable learning rate that would allow time for other academic activities, such as acquisition of skills, would be four to six facts or concepts per hour. Given the potentiality for machine display of these facts and concepts on demand, it would seem justified to enquire as to the appropriateness of the emphasis on the assimilation of facts in medical education.

The foregoing makes clear another characteristic of biomedical data; there are simply too many data to assimilate. To meet our definition of information, all these data have to be analyzed and synthesized. Fortunately, the recovery of biomedical data is less complicated than the numbers suggest. The so-called Bradford-Zipf curve (Figure 2) shows the recovery of articles cited by the peptic ulcer knowledge base as a function of the number of journals. The general shape of the curve is remarkably constant for a large variety of functions and subject matter. It reveals three additional characteristics of biomedical information:

1. A large amount of the important information is concentrated in a relatively few sources.
2. Beyond that, additional information is very expensive to acquire.
3. You can never find all of it.

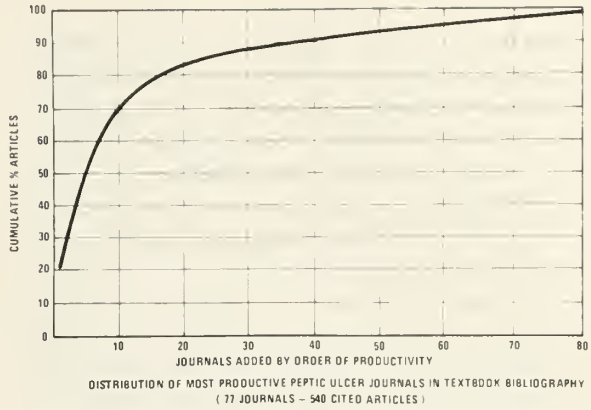

Figure 2.—The Bradford-Zipf curve shows the recovery of articles cited by the peptic ulcer knowledge base as a function of the number of journals.

Models for Organizing Information

So much for attempting to characterize information. Before turning to efforts to model the structure of information, let me remind you of the object of that game. As the amount of information grows, it becomes increasingly difficult to keep track of it, to correct it and to retrieve it when we want it. Clearly, what is needed is some computational or algorithmic method for doing these things. Then we could utilize the enormous power of modern machines to accomplish the task. We have, for example, created tables of logarithms because it was so tedious and arduous a task to do that arithmetic. Since we knew how to generate logarithms, it was better to have someone do it once and for all, and set it down in tables so the rest of us could look it up when we needed it. But because we knew the structure of logarithms when we developed powerful enough machines, we did not ask the machine to store in its memory a table of logarithms and look them up for us. Rather, we simply programmed the machine to do the arithmetic and generate the logarithm, thus even a small pocket calculator can give the logarithm of most numbers.

Unfortunately, as stated above, we know very little about the structure of information, and cannot yet approach the problem in the same way as with logarithms. Instead, we try to create models that will help us organize information in a manner that makes it easier to keep track of. The model most familiar is, of course, the hierarchical model. In the hierarchical model information is nested usually from the most general to the most specific. In most textbooks the table of contents is constructed in this manner. The hier-

archical model is so pervasive and familiar that many of us adopt it subconsciously, as representing reality. Since structure and function are so intimately related, our concept of the structure of information as hierarchical frequently limits our use of information to those things that can be supported by such a structure. For example, much of our diagnostic thinking is determined by our adoption of a hierarchical structure for our information base. Parenthetically, I might add that the obvious utility and thus great appeal of the hierarchical structure is that its dimensionality is so limited. Rarely does one need more than four or five levels of a hierarchy and that is about the limit of dimensionality that most of us can deal with. Perhaps it would be more correct to say that because most of us cannot deal with a greater dimensionality, we limit the hierarchy to those dimensions and fortunately that is enough to be useful.

The hierarchical model is obviously deficient in structuring relationships across hierarchies as well as those on the same level within hierarchies. In an effort to structure these relationships, as well as those covered by the hierarchy, attempts have been made to trace the relationship in a network fashion. One readily understood effort is through the use of science citation index. Using some fairly simple threshold rules, it is possible to identify through mutual citation and cocitation, a cluster of papers. In such a cluster, there is invariably an identifiable core or central configuration and the content of that paper or papers in the central configuration represents a "fundamental concept." In addition, it is possible by this network mapping to identify relationships between clusters and thus between concepts.

Perhaps a model to which we can more readily relate is that developed by a committee of the College of American Pathologists designed to deal with the concepts of pathology and called a Systematized Nomenclature of Pathology (SNOP).

SNOP constructs a network around four basic nodes: topography, morphology, etiology and function. This systematized nomenclature consists of approximately 15,000 pathology terms in English language form. Each term is assigned to one and only one of the four categories or nodes and given a unique number.

- Topography—a list of names of body sites.
- Morphology—a list of names of structural changes that occur in tissues as a result of disease.
- Etiology—a list of names of causative agents of disease such as microorganisms, drugs and chemicals.
- Function—a list of names of the physiological manifestations associated with diseases plus a limited number of specific infectious diseases.

T2600	M8103	E0000	F0000	Bronchus, Carcinoma
T0000	M0000	E6927	F0000	Tobacco (Cigarettes)
T0000	M0000	E0000	F7103	Paroxysmal Nocturnal Dyspnea
T5600	M8106	E0000	F0000	Liver, Metastatic Carcinoma
T5600	M3850	E0000	F0000	Liver, Hemorrhage
T0000	M7051	E0000	F0000	Cachexia
T0000	M0000	E8816	F0000	Fluorouracil Therapy
.	.	.	.	
.	..	.	.	
.	.	.	.	
Txxxx	Mxxxx	Exxxx	Fxxxx	(Language String)

Figure 3.—A partial example of what a Systematized Nomenclature of Pathology (SNOP) record might look like.

A partial example of what a SNOP record might look like is illustrated in Figure 3.

This translation from English into an artificial language designed to model the structure of relationships between the four nodes achieves a manipulable notation, free from ambiguity that has enormous power particularly for retrieval. In years gone by, we had stacks of cards with holes punched on the perimeter and knitting needles were used to shake out the cards representing relationships. We have come a long way with SNOP. To attempt to generalize to a Systematized Nomenclature of Medicine (SNOMED)[4] two additional nodes are used: disease and procedures.

Clinical Problem Solving

Our concern with the structure of information in a medical school environment is how it may affect medical education. We are concerned with the study of medicine and in particular with inculcating the art and science of clinical problem solving. Problem solving may be thought of as sequential decision making; and decision making is an application of information processing according to some set of specified strategies.

If I were to write the equation $2x-2=0$, most, if not all of you, would immediately say $x=1$. And if I asked how you arrived at that conclusion, I would learn that although you may have taken some shortcuts, in essence, you first subtracted -2 from both sides of the equation yielding $2x=2$ and then divided both sides by 2 yielding $x=1$. For this limited set, the rules can be written generically as—given x as a variable and N is a number—

If $x=$ N, Stop!

If N is on the left side of the equation, then subtract N from both sides.

If x on the left side of the equation has a coefficient a where $a \neq 1$, then divide both sides by a.

This is clearly problem solving by sequential decision making through information processing according to some set of specified strategies. In computer language these strategies are called *production rules.*

If we assume this to be representative of human problem solving, we can make a number of observations:

1. We solve problems by a remarkably small number of manipulations of information. We read symbols, we write symbols, we store them in memory, we copy them, we compare them for equality or inequality, and we substitute one set of symbols for another. This is exactly how machines solve problems.

2. We do these manipulations according to a preset but by no means unique strategy. That is, there are clearly other ways to solve this problem. Therefore, it is clear that our strategies are culture bound. They depend in this instance on the strategies we have been taught in our algebra course.

3. We notice immediately that there is a clear unambiguous stopping rule. As a matter of fact, it is stated first. If $x = \mathrm{N}$—stop! The problem is solved! No additional information or manipulation is required or desired. Since the process is obviously an iterative one, this stop rule is critical —otherwise, we become entrapped in endless reverberating cycles.

Now obviously, the structure of the network of relationships of numbers is well understood. We can readily compare and substitute, and in so doing be confident of the consequences. When the information we are manipulating is represented by words, the results of comparisons are not always clear—nor are the effects of the other manipulations. Still, we are essentially limited to these devices, so we do the best we can and we attempt to compensate with a wide range of constantly changing strategies.

Before examining briefly some of the strategies for problem solving, it is important to recognize that humans also employ a strategy about strategies. They initially tend to employ the strategy with which they are most familiar and usually most comfortable. But they also frequently switch strategies or adopt shortcuts (new strategies), not so much because the original strategy would not yield a solution, but rather because in the course of execution they recognize a condition that simplifies the problem and facilitates the solution. Two or three brief examples may be helpful.

If the problem is to multiply 37 by 23, most persons, either in their heads, or with paper and pencil will set out to apply the rules of multiplica- $3 \times 7 = 21$, $3 \times 3 = 9 + 2 = 11$, and so forth. However, one or two may simply immediately say the answer is 851. This immediate response is not a manifestation of extraordinary facility with arithmetic nor an extraordinary memory of having at some previous time produced that product. Rather, the immediate response is because of the perception that the problem can be converted to another problem which is far less tedious to solve; namely, the product of $(30+7)(30-7)$. We remember from algebra that $(a+b)(a-b) = a^2 - b^2$. Therefore, $37 \times 23 = 900 - 49 = 851$. Almost everyone begins his study of interpretation of electrocardiograms with electrophysiology. The method, however, that he rapidly substitutes is pattern recognition. Still, when he cannot recognize the pattern, he returns to electrophysiology to try to interpret the tracing.

Although there is some tendency to teach medicine in terms of all possibilities, for example, the 13 (if it still is 13) causes of nephrotic syndrome, the 57 causes of pulmonary fibrosis, the differential diagnosis of hepatosplenomegaly, we almost never, and then only as a last resort, employ the problem solving strategy of examining all possible solutions.

Simon[5] has postulated that given a novel problem, humans tend to approach the solution in accordance with three principles. First, they employ a heuristic method. Second, the heuristic method or strategy usually takes the form of means-ends analysis. By this term, Simon means, given a goal and a situation, one finds the difference between them, then retrieves an operator from memory that will reduce that difference; we then apply the operator, thus creating a new situation; we continue to repeat the process until the new situation is identical with the goal. Third, human heuristic problem solvers do not pursue multiple branches of a search tree simultaneously. Rather, they pursue a single branch in depth with very little branching. Only when the search is unsuccessful do they back up and proceed along a different branch.

Experiments with computer problem solving programs show that this deep search strategy is not very efficient. However, the efficient strategy, so called "best first" method, calls for a large short-term memory to keep track of the search in multiple dimensions. Humans simply do not have a large enough short-term memory to be able to adopt this method.

Simon's principles also contain an explicit stopping rule when the new situation is identical with the goal or the difference between them is zero. STOP.

Applying Findings

Given a situation represented by the patient's clinical and laboratory findings, which presumably represent something other than health (disease), our goal is to restore the patient to something other than disease (health). We employ a variety of strategies, usually heuristic, to reduce the differences between the situation and the goal. The common heuristic is to start with an attempt to put a name (diagnosis) on the array of information the patient provides. We know that if we succeed, we will have but translated the problem into a notation that is more easily manipulated and more specifically indicates relationships. But if that strategy fails, we adopt another strategy directed at what we call symptomatic therapy.

Our strategies are usually heuristic because our notation is so imprecise it does not lend itself to algorithmic manipulation. But occasionally, we adopt a heuristic strategy because it is quick and convenient. Still our impulse is to believe there is something highly desirable about algorithmic decision making. Therefore, if given the opportunity when the pathophysiology is known, we almost always transpose to a manipulable notation to employ an algorithm. For example, such manipulable notations exist for some clinical chemistry and pulmonary physiology situations. Where we employ algorithms, we usually follow the stop rule implicit in the algorithm. But when we apply heuristic methods, we rarely invoke a stop rule. One reason is that rarely do we succeed in reducing the difference between the situation and the goal, all the way to zero. For example, not all of the findings are explained by the diagnosis. But even if we do succeed in explaining all the findings, we rarely stop; perhaps because we are not convinced that the solution is unique; perhaps because our own work and belief rejects the solution or prefers another; perhaps because the known consequences of being wrong are grave and we simply want to be sure.

Therefore, we seek more information. But now we no longer have an explicit stop rule. Indeed, we also have no intuitive strategy because the difference between the situation and the goal is already zero. So we really have only two choices. In essence, repeat what we already have done or reformulate the situation, or the goal, or both. If more than one diagnosis explains the findings, we may restate the goal from finding the diagnosis that explains the findings to finding the most likely diagnosis that explains the findings (by most likely we mean the one with the highest probability in the frequency sense). Or we might restate the goal to finding the diagnosis for which there is a therapy, even if it is not the most likely.

I do not wish to belabor the point or to go deeper into decision-making strategies. I wish merely to illustrate that information processing is fundamental to a major portion of the medical endeavor. This discipline or science about which so much more needs to be learned is so intrinsic to the purposes of medicine that it deserves to be recognized as a basic science in the same sense as anatomy or biochemistry.

I am reminded of a paper by an English investigator named Miller.[6] He reported that assimilation of information in a lecture begins to diminish after 15 minutes, and after 30 minutes the amount absorbed is practically zero. The theory suggests, however, that for a moment your attention may be recaptured by the phrase *in conclusion*. Therefore, in conclusion, I have tried to suggest that the discipline of information processing is fundamental to the medical endeavor. I would remind you that nowhere does that basic science appear in the medical curriculum, no organizational element exists in the medical school to house those who would pursue this discipline, and no career development or career identification fosters and attracts either research or education in the pursuit of this discipline.

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Refer to: Tupper CJ: Scope of practice (Information). West J Med 1982 Nov; 137:467-468

Information

Scope of Practice

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THE MEDICAL PROFESSION today must constantly monitor the many interactions among patient care, the medical profession and legislation. Legislation is made by the Congress, by state legislatures, by regulatory agencies and by the courts. These activities are monitored by organized medicine at all levels with the American Medical Association being the most influential at the federal level and state medical societies at the state level.

All of us are familiar with legislative bills introduced in many states to extend the scope of practice by statute. Such legislation varies from state to state, but there has been a continuing trend for expansion of scope of practice in this fashion. The use of drugs by optometrists is but one example. Others include expansion of the scope of practice of nurse anesthetists, nurse midwives and many other practitioners.

However, there are a number of other techniques whereby nonphysician practitioners attempt to improve their position—expand their scope of practice—without altering the statutory statement of lawful professional activities in which the practitioner may engage. For example, in California a bill proposed to allow a psychologist to serve as clinical director of a state hospital for the mentally disordered, a position presently reserved to a qualified physician. Another bill sought to permit psychologists to examine peace officer job applicants for the purpose of determining their mental health, a task presently reserved to physicians. Still another bill proposes to mandate participation of psychologists in individual practice arrangements (IPA's) that provide mental health services. Thus, one can expand one's scope of practice by gaining authority to hold a position or occupy a work role previously reserved to physicians.

Other devices for improving the midlevel practitioners' lot are available. Statutes limit the maximum body of activities that a licensed health care provider may provide. However, there are certain nonstatutory limits on a practitioner's activities that, in fact, may circumscribe those activities to something less than what is authorized by statute. For example, if hospital regulations or protocols do not provide a place for a midlevel practitioner to carry out a procedure that can be done safely only in a hospital setting, then that practitioner's scope of practice is thereby somewhat narrower than lawfully authorized. Similar practical constraints are imposed by restrictions on Medicaid reimbursements and on compensation by private insurance plans. A midlevel practitioner who is not paid for a particular procedure likely will not do that procedure, and his or her scope of practice is reduced accordingly.

Midlevel practitioner groups are becoming more and more aware of the many means by which to increase their roles and expand their practices without statutory action. Medicine must develop a sensitivity to these devices and activities and must be prepared to develop policy in response to them. The indirect means of achieving an expanded scope of practice include the following:

- Mandating or authorizing Medicaid or other public reimbursement of services.
- Mandating coverage of services by private insurance, or mandating the offering of coverage by private health insurance plans.
- Authorizing the performance of health care services in specified facilities or clinics, without authorization to render such services in other settings.
- Requiring the inclusion of limited-license professionals in health care organizations, groups and plans.
- Mandating the membership of limited-license personnel on the staffs of hospitals and other facilities, or as members of "health care teams."
- Changing license titles to imply a new or greater ability to render health care services (for example, a proposal to change marriage, family

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and child counselors to marriage and family *therapists*.)

• Assigning academic or licensing titles that carry prestige beyond the holder's competence (for example, a proposal to license *doctors* of mental health; the term "doctor" connoting the highest level of expertise).

• Mandating reimbursement rates for services at parity with payment for physicians, connoting parity of quality of services and equal competence of providers.

• Enlarging the programs for payment of services to include limited-license practitioners not previously covered; for example, extending crippled children's coverage to providers previously covered only by Medicaid.

• Elevating training standards and requirements, followed by demand for expanded license authority.

• Development of and participation in health manpower pilot projects, the almost inevitable result of which will be a demand for expanded scope of practice or an enhanced role in health care delivery.

• Development of "career ladder" programs, the climbers seeking expanded scopes of practices as they perceive success in mounting the projected ladder.

• Modification or lowering of license requirements whereby persons previously unable to meet licensing or examination standards now qualify for licensure.

Medicine must keep itself continually aware of the indirect means by which limited-license practitioners may seek to enhance their role in health care, and should oppose any legislation and regulation which attempts to do so inappropriately.

Refer to: Werner SB: Sources of supply of selected immunobiologics: 1982 (Information). West J Med 1982 Nov; 137: 468-470

Information

Sources of Supply of Selected Immunobiologics: 1982

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INFORMATION on the availability and sources of new or infrequently used immunobiologics can be hard to obtain. Private practitioners and public health departments in California and elsewhere in the western states occasionally call the Infectious Disease Section of the California Department of Health Services in their search for these immunobiologics. We last published information about rarely used biologics in the February 1979 issue of THE WESTERN JOURNAL OF MEDICINE. As there have been so many changes since then, updated information is called for.

As we stated before, we may not have identified *all* producers of the materials listed but we have made an exhaustive effort before stating that an immunobiologic material is "not available." This writer would appreciate, however, any corrections or additions that are now known, or become known, so that the list can be kept up-to-date.

We emphasize that the California Department of Health Services in no way endorses the products or manufacturers that are mentioned, nor do we necessarily recommend that any of these products be used. Staff members of the state's Infectious Disease Section remain available for consultation on these biologics and their use ([415] 540-2566).

SKIN TEST ANTIGENS

Blastomycosis*
Not available.

Brucellergen (brucellosis*)
Not available.

Cat scratch fever
Unlicensed antigen, available only by special arrangement with S. S. Kalter, PhD, Southwest Foundation for Research and Education, P.O. Box 2296, San Antonio, TX 76902, (512) 674-1410.

Coccidioidin*

1. Berkeley Biologicals, 1831 Second Street, Berkeley, CA 94710, (415) 843-6846 (for Spherulin).

From the Infectious Disease Section, California Department of Health Services, Berkeley.

Submitted August 9, 1982.

Reprint requests to: S. Benson Werner, MD, Infectious Disease Section, California Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704.

2. Iatric Corp., 2330 South Industrial Park Drive, Tempe, AZ 85282-1893, (602) 966-7248.

Diphtheria toxin (Schick Test)
Massachusetts Public Health Biologic Laboratories, 375 South Street, Boston, MA 02130, (617) 522-3700.

Echinococcin* (Casoni)
Tropical Disease Lab, 1617 HSW, University of California Medical Center, San Francisco, CA 94143, (415) 666-2166, 666-2167, or 666-2510.

Filariasis*
Not available.

Histoplasmin*

1. Parke-Davis, 201 Tabor Road, Morris Plains, NJ 07950, (201) 540-2117, 540-4241, or 540-4243.
2. Berkeley Biologicals, 1831 Second Street, Berkeley, CA 94710, (415) 843-6846.

Kveim (Sarcoid)
Ph. Leuenberger, MD, Division de pneumologie, CHUV, 1011 Lausanne, Switzerland.

Leishmaniasis*
Not available.

Lepromin (leprosy)
Not available.

Lymphogranuloma venereum (Frei test)*
Not available.

Mumps*
Eli Lilly and Co., Indianapolis, IN 46206, (317) 261-3377.

Scarlet fever toxin (Dick test)
Not available.

Schistosomiasis*
Not available.

Toxoplasmosis*
Not available.

Trichinella*
Not available.

Tularemia*
Not available.

VACCINES

Anthrax
Prepared by Michigan Department of Public Health Laboratories, Lansing, MI 48909, (517) 373-1290, and available to MD's from Division of Host Factors, CID, CDC (404) 329-3356, or the Michigan Department of Public Health Laboratories.

BCG (bacillus Calmette-Guérin)
Prepared by Glaxo Operations, U.K., Limited, Greenford, Middlesex, England and distributed by Glaxo Inc., 1900 West Commercial Boulevard, Ft. Lauderdale, FL 33309, (305) 776-5300.

Hepatitis B
Merck, Sharp & Dohme, West Point, PA 19486, (215) 661-5000.

Meningococcus

1. Tetravalent (A/C/Y/W-135) vaccine prepared by Connaught Laboratories, Inc., Swiftwater, PA 18370 and distributed by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034, (609) 424-3700 or (800) 257-8349.
2. Bivalent (AC) vaccine by Merck, Sharp & Dohme, West Point, PA 19486, (215) 661-5000.

Plague
Cutter Laboratories, 4th and Parker Streets, Berkeley, CA 94710, (415) 420-4000 or (800) 352-5495.

Polio, inactivated (Salk)
Connaught Laboratories Limited, Ontario, Canada and distributed by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034, (609) 424-3700 or (800) 257-8349.

Rabies, duck embryo vaccine (DEV)
Not available.

Rabies, human diploid cell strain (HDCS) origin
Merieux Institute, 1200 NW 78th Avenue, Suite 109, Miami, FL 33126, (800) 327-2842.

Rocky Mountain Spotted Fever
Not available.

Typhus
Not available.

Yellow Fever
Connaught Laboratories, Inc., Swiftwater, PA 18370, and distributed by A. H. Robins, Inc., 7500 Darby Town Road, Richmond, VA 23231, (800) 446-9824 to State-registered Yellow Fever Vaccination Centers authorized to purchase vaccine.

ANTITOXINS AND IMMUNOGLOBULINS

Botulism antitoxin *(equine)* (Trivalent ABE)
Connaught Laboratories Limited, Ontario, Canada. Available from California Department of Health Services, Infectious Disease Section, by supply from Division of Host Factors, CID, CDC. There are also emergency stockpiles stored at Foreign Quarantine stations in the USA which may be released on notifying the Division of Bacterial Diseases, Center for Infectious Diseases, CDC. The day number is (404) 329-3553 and the night and holiday number is (404) 329-2888.

(Bivalent AB)
Not available.

Diphtheria antitoxin *(equine)*

1. Connaught Laboratories, Inc., Swiftwater, PA 18370 and distributed by Elkins-Sinn, Inc., 2 Esterbrook Lane, Cherry Hill, NJ 08034, (604) 424-3700 or (800) 257-8349.
2. Michigan Department of Public Health Laboratories, Lansing, MI 48909, (517) 373-1290.
3. Sclavo, Inc., 5 Mansard Court, Wayne, NJ 07470, (201) 696-8300 or (800) 526-5260. There are emergency stockpiles stored at Foreign Quarantine stations in the USA that can be released by calling the Division of Immunization, CDC (404) 329-3091 daytimes and (404) 329-2888 nights and holidays.

Gas gangrene, polyvalent
Not available.

Hepatitis B immune globulin (HBIG), human

1. Abbott Laboratories, Abbott Park, North Chicago, IL 60064, (800) 323-9100.
2. Alpha Therapeutic Corp., 5555 Valley Boulevard, Los Angeles, CA 90032, (213) 440-0800.

*Serologic tests are also available (through local or state health department laboratories).

3. Cutter Laboratories, 4th and Parker Streets, Berkeley, CA 94710, (415) 420-4000 or (800) 352-5495.
4. Merck, Sharp & Dohme, West Point, PA 19486, (215) 661-5000 or (215) 661-5962.

Mumps immune globulin
Not available.

Rabies immune globulin (RIG), *human origin*

1. Cutter Laboratories, San Lorenzo, CA (415) 276-8200 or (800) 352-5495.
2. Seralc Corporation, Miami, FL, and distributed by Merieux Institute, 1200 NW 78th Avenue, Suite 109, Miami, FL 33126, (800) 327-2842.

Snake antivenin, *(equine)* rattlesnake, copperhead and moccasin
Wyeth Laboratories, Wasp and Biddle Streets, Marietta, PA 17547, (717) 426-1941.

Snake antivenin, *(equine)* North American coral snake
Wyeth Laboratories, Wasp and Biddle Streets, Marietta, PA 17547, (717) 426-1941.

Spider antivenin, *(equine)* black widow spider
Merck, Sharp & Dohme, West Point, PA 19486, (215) 661-5000.

Staphylococcal antitoxin
Not available.

Tetanus immune globulin

1. Alpha Therapeutic Corporation, 5555 Valley Boulevard, Los Angeles, CA 90032, (213) 440-0800.
2. Cutter Laboratories, 4th and Parker Streets, Berkeley, CA 94710, (415) 420-4000 or (800) 352-5495.
3. Hyland Therapeutics Division, Travenol Laboratories, Inc., 444 West Glenoaks Boulevard, Glendale, CA 91202, (213) 956-3200 and distributed by their Customer Operations Department, One Baxter Parkway, Deerfield, IL 60015, (312) 480-5057.
4. Wyeth Laboratories, Wasp and Biddle Streets, Marietta, PA 17547, (717) 426-1941.

Vaccinia immune globulin (VIG)
Hyland Therapeutics Division, Travenol Laboratories, Inc., 444 West Glenoaks Boulevard, Glendale, CA 91202, (213) 956-3200, ext. 5470.

Varicella-zoster immune globulin (VZIG)
Massachussetts Public Health Biologic Laboratories, 375 South Street, Boston, MA 02130, (617) 522-3700 and distributed in Massachusetts by the producer, and elsewhere in the United States and Canada by the American Red Cross Blood Services-Northeast Region, through 18 regional blood centers. For information on the center serving your area, call (617) 731-2130 or (617) 734-4430, 24 hours/day.

BOOK REVIEWS

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

THE ELBOW—Edited by Thomas G. Wadsworth, MChOrth, FRCS, FRCSE; Foreword by S. Benjamin Fowler, MD. Churchill Livingstone Inc., 19 West 44th Street, New York, NY (10036), 1982. 354 pages, $50.00,

This book presents an extensive amount of information relating to the elbow joint and its approximate structures. The editor and other authors are generally well known to orthopedic surgeons in the United States.

There are ten sections or chapters with a total of 354 pages. The information presented represents a wide scope from embryology through biomechanics, pathology, and diagnosis and treatment of disease and injuries. Each section is the work of different authors, which could have resulted in loss of continuity and duplication of information. The editor, however, has blended these sections into a cohesive unit.

The volume is an attractive, well-bound book with clean, well-spaced print on durable semigloss paper. Each page is double columned, promoting ease and rapid reading. The illustrations are clear and appropriate but slightly out of phase as relates to the text.

This book is a valuable addition to any medical library. It is of most value to orthopedic surgeons in training or practice. It is not appropriate for a quick "how to" reference for general physicians.

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CURRENT PEDIATRIC DIAGNOSIS & TREATMENT—Seventh Edition—C. Henry Kempe, MD; Henry K. Silver, MD; Donough O'Brien, MD, FRCP, and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1982. 1,106 pages, $26.00.

The title of this textbook is most appropriate; the editors and contributors have again provided a thorough revision of the earlier edition. The information contained is indeed current and the scope includes virtually all topics of importance to the pediatrician and others responsible for providing child health care. The stated goal of providing "an up-to-date reference and study resource for all child health professions as well as for students and house staff in pediatrics and family medicine" has been fully met.

Chapters and sections worthy of special comment include the thoroughly revised chapters on newborn infants, bacterial and spirochetal infections, nutrition, developmental and learning problems, genetic and chromosomal disorders and immunology. The chapter concerning parasitic infections will be particularly useful for those responsible for the care of children recently entering the United States and those dealing with mycotic infections and unusual forms of bacterial and viral disease will similarly be particularly valuable for those dealing with children with impaired resistance.

The "new diseases" and recently recognized variants of well-known clinical entities have been covered accurately and concisely. The chapter on drug therapy provides a useful guide, but must be supplemented by the specific information provided in package inserts.

Many tables and diagrams are supplied that offer useful summaries of the data as presented and the inclusion of numerous pertinent and current references extends the value of this text substantially. Thus additional information is made available should more background or more detailed information be needed by the reader. A complete and detailed index is provided to assist the reader in locating specific areas and related topics readily.

This text includes a remarkable amount of information and it is perhaps the greatest bargain in pediatric texts today. Every library, clinic and pediatrician's office should have access to this book, and it will be consulted frequently.

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OFFICE GYNECOLOGY—Second Edition. Edited by Robert H. Glass. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD (21202), 1981. 360 pp, illustrated, $32.00.

The office practice of gynecology is the most frequent patient contact between the female patient and the physician. Unfortunately, it also is the least mentioned in standard textbooks of gynecology.

Office Gynecology by Dr. Glass is an excellent attempt to overcome this deficiency. He has put together a group of outstanding physicians and has developed a comprehensive view of office gynecology. This is the second edition and chapters on antenatal diagnosis, benign breast disease, primary dysmenorrhea, urinary tract infections and nutrition have been added. These new chapters make the second edition a much better book as they further scan the scope of office practice for the physician.

The book is easy to read and the authors have given each of their presentations in a logical format. If there is any criticism it is that the material appears less thorough than usually seen in a standard textbook. However, the book does give an excellent overview and, for physicians who desire greater detail, most chapters have references.

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ULTRASTRUCTURAL APPEARANCES OF TUMORS—A Diagnostic Atlas—Douglas W. Henderson, MB, BS, FRCPA, and John M. Papadimitriou, MD, PhD, MRCPath, FRCPA; Foreword by Richard L. Kempson, MD. Churchill Livingstone Inc, 19 West 44th St., New York, NY (10036), 1982. 409 pages, illustrated, $89.00.

The electron microscope has extended the observational capacity of histologists, whether interested in normal structure or disease. In the latter instance, pathologists have applied these techniques, successfully, to a variety of disease states, including neoplasms. These authors have compiled in a single text, both a catalogue of information concerning ultrastructural features of neoplasia and representative samples taken therefrom. They start with the premise, a valid one, that the ultrastructural appearance of cancer has not provided diagnostic differentiation between proliferative lesions of a

variety of types, but does provide interesting clues to the biology of the lesions observed. In point of fact, in several instances, specific intracellular organelles support evidence of a specific tumor type, those derived from the neurosecretory endothelium are a classic example. Their review is extensive, their pictures great in number and their references, contemporary. The use of tabulation to indicate specific structures that may or may not appear in different tumor types will aid those who wish to separate the information available, and aid and help in diagnosis. For a pathologist without access to an electron microscope, this is an interesting travelogue through abnormal cell structures. For a pathologist with an available electron microscope, this text provides a reference source in which to develop information necessary to separate tumors with which he may be confronted.

A potential omission is a critical discussion of fixation and embedding, and the added data derived from histochemistry and cytochemistry that might aid in diagnosis of specific lesions. Another particular area that would require some addition is a better description of available information concerning the presence of viruses in these neoplastic cells. This is dismissed very briefly in the introductory chapters.

The book also suffers from lack of attention to freeze-fracture replication in general and the application of freeze-fracture for cell junction identification in particular. In attempting to distinguish mesenchymal and epithelial tumors, the identification of tight junctions (zonelae occludentes) clearly indicates the epithelial origin of the neoplasm. In distinguishing poorly differentiated hematopoietic or lymphoid neoplasms from solid-connective tissue tumors, the existence of gap (communicative) junctions clearly supports the latter genesis.

Not all micrographs are of similar quality, but in general they are first rate. There are some whose size is sufficiently small and whose magnification is sufficiently low so that the details of structure are hard to find. The labeling in some micrographs also leaves something to be desired, and the use of dark letters on dark background requires a search for the label. The addition of ultrastructural examinations as an investigative tool is not stressed, in fact, it is partially dismissed in the text. In spite of these shortcomings, the authors are to be credited for putting together a remarkable text with a wealth of information, not only for those active in diagnosis but for those who may be involved in caring for patients whose diseases are specified by these ultrastructural techniques.

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PAEDIATRIC CARDIOLOGY—Volume 4: Proceedings of the World Congress of Paediatric Cardiology held in London in 1980— Edited by M. J. Godman, MB, ChB(Edin), FRCP(Edin); Foreword by Fergus J. Macartney, MB, BChir, FRCP, and Jane Somerville, MD, MB, BS, FRCP. Churchill Livingstone, Inc., 19 West 44th St., New York, NY (10036), 1981. 788 pages, $79.00.

This book contains the Proceedings of the World Congress of Paediatric Cardiology held in London in 1980. The following major topics are discussed: etiology and pathogenesis of congenital heart disease, clinical and experimental; growth and remodeling of the pulmonary circulation in congenital heart disease; disorder and dysfunction of the myocardium: a changing spectrum; simple approach to the diagnosis and naming of complex congenital heart disease; today's management of the newborn with heart disease; new methods of investigation; computers in pediatric cardiology; natural and unnatural history of congenital heart disease; advances in pediatric cardiac surgery; surgery for complex congenital heart disease; management of the child after cardiac surgery; fate of apparently successfully treated survivors of congenital heart disease; child destined for adult heart disease—potential for prevention; geographic heart disease; cardiac involvement in general pediatric illness; problems in congenital heart disease—today and tomorrow.

As is the case with most if not all publications that represent proceedings of meetings, the style (and quality) varies considerably from one chapter to another. Much, probably most, of the material has been published elsewhere in some form. The quality of the illustrations varies from excellent to poor (for example, the electrocardiogram on page 241 has a number of extraneous blots and marks on it and should not have been published). Some of the angiocardiograms are blurred. A number of mistakes are present in the bibliographies.

Despite these minor criticisms, this book will be of interest to pediatric cardiologists and to cardiac surgeons. This should not be (nor was it meant to be) a standard reference text. While it does not substitute for an advanced textbook of pediatric cardiology and is quite expensive, it should be considered for the library of pediatric cardiologists—as a luxury, not a necessity.

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ANNUAL REVIEW OF NUTRITION—Volume 1—William J. Darby, Nutrition Foundation, Editor; Harry P. Broquist and Robert E. Olson, St. Louis University, Associate Editors. Annual Reviews Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1981. 510 pages, $20.00 (USA), $21.00 (elsewhere).

Publications in basic and applied nutrition appear at an ever increasing rate, yet the *Annual Review of Biochemistry* last presented a separate treatment of nutrition in 1964. Annual Reviews has now developed this new series to meet the need for critical review of current nutritional research topics.

To that welcome end, the editors have selected for inclusion in the first volume subjects that range from ethical issues in the world food problem to the use of germ-free animals in nutritional studies. Among the 18 articles are 3 that concern iron (assimilation systems in microorganisms, dietary bioavailability and bioavailability from milk), two on nonessential nutrients (choline and taurine), two on food toxicology and two on health effects of various trace elements in the water supply.

Most of the chapters focus on basic nutritional research in laboratory animals or bacteria, with scant attention paid to applied clinical aspects. Thus, the articles on flavoproteins and carotenoids describe biochemical enzyme mechanisms and methods of analysis but scarcely mention the role of the vitamins in health and disease. The exciting current research on the role of carotenes and vitamin A in cell differentiation and development (and, perhaps, in cancer prevention) would seem of greater interest to the general reader.

The few articles that do emphasize clinical nutrition, however, are especially worthwhile. The review of fructose nutrition by Wang and van Eys includes an excellent critical evaluation of the use and misuse of this sugar in diabetes care. Rothwell and Stock take special pains to explain why their studies of weight control by increased energy expenditure in animal model systems cannot be applied easily to humans.

Despite these and other important exceptions, the first volume of *Annual Review of Nutrition* is most likely to

interest academic nutritionists. Perhaps the editors will select more applied topics for future volumes. Until they do, continue to consult Annual Review of Medicine (and other sources) for the latest word on nutrition in clinical practice.

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PHYSICIAN'S HANDBOOK—Twentieth Edition—Marcus A. Krupp, MD; Lawrence M. Tierney, Jr, MD; Ernest Jawetz, MD, PhD; Robert L. Roe, MD, and Carlos A. Camargo, MD. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1982. 774 pages, $12.00.

Krupp's *Physician's Handbook* was introduced in 1941. It has been a widely read smorgasbord of quick reference for anyone seeing patients with general problems. I read it in medical school, reread it in residency and continue to read it as a practicing family physician. It occupies a venerable place in the ready-reference section for the office.

The book begins with a comprehensive discussion of the emergency medical examination and then has an outline for basic history taking and physical examination. This is especially valuable for medical students who wonder, "Have I missed anything?"

Laboratory evaluation is comprehensively discussed in 250 cogent pages. This is followed by a further distillation of material on vitamins, fluid and electrolyte balance, and oxygen and respiratory therapy.

An especially valuable table is that showing the current clinical uses of radioactive isotopes. Other tables, charts and illustrations are accurate, well-conceived and clear.

A surprising inclusion is the discussion on medical genetics. I don't remember this existing when I was in medical school but it has certainly become an important area to recognize for family physicians.

Who will read this book? Medical students, residents in family practice, paraprofessionals and midlevel practitioners will find it very valuable. Also, anyone who has read earlier editions in the past will find this new one readable as well as filling the need for immediate knowledge.

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WILLIS'S OXFORD CASEBOOK (1650-52)—Introduced and edited by Kenneth Dewhurst, TD, MD, DPhil, FRCPsych. Sandford Publications, Manor House, Sandford-on-Thames, Oxford OX4 4YN, England, 1981. 199 pages, 12 English Pounds, limited to 750 copies.

For those many physicians who live under the impression that medical history is composed of biographies, hero worship and anecdotes about several selected great doctors, this book will be a delightful revelation because it represents the essence of what the history of medicine should be. Needless to say, there is scarcely any physician today who is not familiar with the name of Thomas Willis, father or founder of neurology, and the description of his famous "circle." It is less likely though that physicians nowadays are familiar with the fact that Thomas Willis had an extensive and general medical practice and saw and treated many patients with a vast variety of afflictions. These included respiratory diseases, gastrointestinal disturbances, kidney disease and stones, venereal diseases and various forms of arthritis, gout and rheumatism.

Dr. Dewhurst who studied and published *Thomas Willis's Oxford Casebook* did an inspired job in deciphering and transcribing Willis's detailed notes which he dashed down in the uneven rhythm of his carriage, each time he left the house of a patient. Judging from the reproduction of one such page from *Willis's Casebook,* Dr. Dewhurst's familiarity with Willis's handwriting and mode of thinking must have enabled him to read and anticipate information that would have been illegible to most others.

From the *Casebook* we learn that Thomas Willis followed the medical practices of his day: he bled his patients, but generally he only "took a little blood," he gave them herbal medications, including opium and laudanum. In contrast to many physicians of the past Willis gave his prognosis very frankly, and often too pessimistically, so as to allow his patients the time to see their clergymen, and to settle their worldly affairs.

Of special interest is Dr. Dewhurst's "Summary of Willis's Casebook" during the years of his practice at Oxford 1650-1652. During this period he evidently was very generous in making housecalls; he saw 50 patients, many of whom he visited repeatedly, 20 of whom were men, 22 women and 8 children.

Willis's specialty distribution ranged over the various branches of medicine, including dermatology and venereal disease, and contagious diseases, including all the fevers that were then endemic or epidemic. Willis also operated on patients and saw a great variety of psychiatric patients. The radius of distance of his practice extended as far as 25 to 57 miles, although most of his patients were located between 6 to 16 miles away from his home base.

On the whole, this book presents an intimate and thorough insight into 17th century medical practice; it also contains a chronological outline of Willis's life and career. In addition, there is an excellent biographical sketch of Willis.

The book concludes with a brilliant "Summary and Conclusions," which contain the essential facts of the life and work of the "founder of neurology."

I can scarcely think of anyone in medicine, medical history or the auxiliary professions to whom this book would not be of value and abiding interest.

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ANNUAL REVIEW OF NEUROSCIENCE—Volume 5, 1982—Editor: W. Maxwell Cowan, MD; Associate Editors: Zach W. Hall, PhD, and Eric R. Kandel, MD. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1982. 392 pages, $22.00 (USA), $25.00 (elsewhere).

The fifth volume in this series contains articles of interest to both practicing physicians and basic neuroscientists. This is not new; previous editions have been similarly broad in scope. However, this volume also contains a symposium, from the Society for Neuroscience, on the scientific origins of modern neuroscience. This symposium is of more than passing interest to students of neuroscience.

Two articles in this volume are directly useful to clinical practitioners. Brady reviews the classification, clinical features and biochemistry of inherited metabolic storage disorders. This article also contains an interesting preview of potential therapies for these illnesses. McKhann reviews the pathophysiology of multiple sclerosis, with emphasis on immunopathology.

There are several articles in this volume which are of interest to basic neuroscientists. Iggo and Andres review current ideas about the morphology and function of cutaneous receptors. Two articles review the physiology of joint and muscle proprioception, with a historical tip of the hat to Sherrington. Cerebellar physiology and its

influence on the vestibulo-ocular reflex is reviewed by Ito. The biology of human memory, both normal and abnormal, is described by Squire. Other chapters cover electroreception, the technology of intracellular perfusion and the comparative molecular biology of cholinesterase.

The symposium on the origin of modern neuroscience contains several articles which are both charming and interesting. John Eccles contributes a description of the historical and scientific aspects of the discovery of chemical transmission at the synapse. In this, the best article in the volume, he gives a personal account of the theoretical and experimental development of this very important advance. The biology of nerve growth factor and the neurophysiology of squid axon membrane are also discussed. Finally, Hubel contributes what he describes as a "slanted historical perspective" on the origins of cortical neurobiology.

This volume contains articles of considerable importance. The authors are certainly authorities on their subjects (including several Nobel laureates). It is enthusiastically recommended for both basic and clinical workers in the field.

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DOUGLAS-STROMME OPERATIVE OBSTETRICS—Fourth Edition—Edward J. Quilligan, MD, and Frederick Zuspan, MD; contributions by William J. Ledger, MD; Barry S. Schifrin, MD, and Feizal Waffarn, MD. Appleton-Century-Crofts, 292 Madison Avenue, New York, NY (10017), 1982. 967 pages, $68.50.

This excellent book has been a standard in its subject matter for many years. Drs. Quilligan and Zuspan, with the aid of other contributors, have updated it, making it an even more useful learning resource. As with past editions, the chapters concerned with surgical approaches to obstetrical problems are extremely complete, clearly written and very practical. These include the chapters covering the control of pregnancy loss, abortion, ectopic pregnancies, induction of labor, surgery related complications, third trimester bleeding, management of labor and delivery complications, use of forceps, cesarean section, trauma associated with delivery, and postpartum and postabortal complications.

The chapter on medical complications of pregnancy is extremely useful with good advice for current management of a number of typical problems. This material has been a particular interest of Dr. Zuspan and is handled very well.

The chapter on fetal monitoring, which was written by Dr. Barry Schifrin, also is very useful. The format allows for the answering of specific questions raised by monitor tracings and suggests appropriate management.

The anesthesia chapter is an excellent and up-to-date review of obstetrical anesthesia and the chapter concerning the immediate management of the asphyxiated infant written by Dr. Feizal Waffarn should be helpful to all obstetricians.

The section on fetal destructive operations is extremely complete and well written. It projects a ghastly specter rarely considered or used in modern obstetrics and, thus, tends to stir a lot of discomfort in today's obstetricians. Nevertheless, it is material that should be understood so that appropriate skills will be available in the occasional instance when they are necessary.

As with any book that has evolved through several editions and has had multiple contributors at different times, a few inconsistencies and anachronisms exist in this text. For example, in chapter 11, the authors make the statement that x-ray pelvimetry is only indicated in breech presentation where vaginal delivery is contemplated. Later in the same chapter, however, it is mentioned as appropriate management in evaluating a persistent posterior position. I imagine Dr. Quilligan wrote the first statement, and those from the past wrote the latter. In chapter 1, a prenatal form from New York Hospital is shown as an example of one that is modern and useful. Today, however, most modern obstetrical units use forms that allow for appropriate risking techniques. Although such approaches are noted later in the book, it would have been nice to see the initial chapter so updated. I would also encourage the authors to continue to update pictures and illustrations that are used in future editions. Many of the ones in the current text are getting a bit old and out of date.

These observations are not meant to be overly critical. I feel the book is an elegant one, which should be very useful to students, residents and practitioners as they manage their obstetrical patients.

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SO YOU WANT TO BE A DOCTOR?: The Realities of Pursuing Medicine As a Career—Naomi Bluestone, MD. Lothrop, Lee & Shepard Books, 105 Madison Avenue, New York, NY (10016), 1981. 256 pages, $12.95.

Students wishing to learn about "the realities of pursuing medicine as a career" (as Dr. Bluestone puts it) have a number of options open to them in the growing literature on medical education. Other than the classic literature about medical students (William Somerset Maugham's *Of Human Bondage*) three types of books seem to abound: there are sociological/political treatises based on research and the author's personal viewpoint (*Medical Mystery* by Steven Jonas); there are psychologically oriented works that attempt to put the "trials and triumphs" of medical school into rational perspective for individuals (*Doctor-To-Be* by James A. Knight) and there are the first-person accounts of medical school (*Gentle Vengeance* by Charles LeBaron).

Information of direct value to medical students attempting to cope with their situations may vary with literary source and format. While first person accounts are facile reading, the reader must extrapolate generalizations from between the lines of a narrative. The other two forms of writing tend to be more factually direct. A problem is identified and possible solutions proffered. Dr. Bluestone attempts to provide this service.

Dr. Bluestone, known for her offbeat columns in *The New Physician*, has written a naturalistic narrative tracing her decision to enter medical school, her experiences as a student and finally her perceptions as a house officer. Interspersed throughout the book are more in-depth explorations of certain personal and social issues, addressed as they arose in the author's own experience. Understandably these issues are not new or strange to one familiar with the process of medical education: the infantilization of the new medical student confronted by a paternalistic educational system; questions about the relevance of some curriculum material; social isolation felt by a professional student ensconced in academic pursuits; the seemingly parochial interests of some of the basic science faculty; the problems posed by the voluminous material presented to medical students, and much more.

In a section entitled "Private Thoughts for Special People" the author muses about the relationship of medical career and education to families of students, minority students and women. Some of this material is drawn from her previous writings in a number of different journals. Bluestone's tone is conversational and humorous, although forced sarcasm and negativity are occasionally evident. This may be of little import in that specific suggestions are made for *coping* with the problems of medical education, but a number of readers will undoubtedly be neither amused nor energized by this approach to the subjects at hand.

The uniqueness of the literature on medical education lies in its variety. While Naomi Bluestone has written a lighthearted and socially liberal book the intellectual fodder is absent, particularly when compared with the recently revised version of *Doctor in the Making* (James A. Knight), a book to which she alludes. The theme of personal awareness and self-knowledge as a desired end is well taken. The search toward this end, however, is a highly individual one and Bluestone does not seem to understand this. The appeal of her book is hardly ecumenical and students may need to look beyond it to find a satisfying literary resource.

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COPING IN MEDICAL SCHOOL—Bernard Virshup, MD. Health Sciences Consortium, Inc., 200 Eastowne Drive, Suite 213, Chapel Hill, NC (27514), 1981. 130 pages, $9.95 (paperback).

In *Coping in Medical School,* Dr. Bernard Virshup is concerned that in becoming physicians, people are dehumanized, brutalized and segmented. Friends of an incoming medical student will warn, "don't go to medical school, you will change." How that change takes place and how to avert the "dehumanizing" process are the subject of this paperback volume. The author focuses primarily on the area of personal needs, these motivating forces shared by every individual person, and points out how, in the setting of a modern medical school, these needs not only are not met but in fact are systematically frustrated. Listing these needs, he includes the following: attachment, independence and identity, self-esteem, security, creativity and actualization. Additional pitfalls for medical students, he points out, are the factors of stress, anger and depression.

To combat these pressures the author urges medical students to increase by all possible means their knowledge of themselves, to be aware of their basic needs and wants and make some realistic arrangement for meeting them, to reach out for a support group of friends and associates, and to reassess their expectations for themselves in a more realistic light. In particular he stresses the importance of self-esteem, "how well you do in medical school will depend on how you value yourself as a worthwhile person . . . if you have to *prove* you're good, you'll be vulnerable."

To deal with the needs and pitfalls he suggests a series of exercises to be done alone or within a congenial group of colleagues. These exercises are not new, he is quick to admit, but rather borrowed from various disciplines, ranging from the quiet centering process of meditation to the role-playing recrimination-and-response techniques of the active group therapies. These exercises, in fact, make up a large portion of the book and, although helpful in indicating some new ways of approaching and unlocking one's personal problems, give the book an unfortunate *cookbook* flavor (simple recipes for every occasion), thus reinforcing a feeling of patness and oversimplification.

Recognizing the realities of the medical school ambience, Virshup states, "if one were to draw up a plan for producing depression in an otherwise reasonably normal individual, medical school would fit the plan. Take a conscientious young person, remove him from his previous associations and support systems and . . . all prior sources of self-esteem. . . . Tell him that any difficulties he has . . . are due to his own inadequacies, reduce all outside stimulation and relaxation . . . remove all channels of expression of feelings . . . deprive him of sleep and defer all satisfaction to an indefinite future. . . ." Should we be surprised that the result is helplessness, hopelessness, alienation and low self-esteem—the hallmarks of depression?

In conclusion he proposes a "self-awareness workbook" (chapter 13) which, while smacking of instant psychotherapy, offers a succinct seven-page outline of self-assessment that is valid for any person in any profession, and which effectively summarizes his thesis. A final chapter suggests some teaching goals to help meet the problems he has highlighted (how to handle mistakes or *failure,* how to deal with feelings and anxiety, and a realistic assessment of a person's individual role and responsibility). This volume may provide some guidelines for student support groups.

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PATHOPHYSIOLOGY: The Biological Principles of Disease—Editors: Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine, University of California, San Francisco; and Samuel O. Thier, MD, David Paige Smith Professor and Chairman, Department of Internal Medicine, Yale University School of Medicine—Volume I of INTERNATIONAL TEXTBOOK OF MEDICINE. W.B. Saunders Company, West Washington Square, Philadelphia (19105), 1981. 1,918 pages, $65.00 US; $78.00 Canada.

The book represents a monumental undertaking by two distinguished professors of medicine to summarize the pathophysiologic underpinning of the practice of clinical medicine. To assist them, they have solicited contributions from a knowledgeable and authoritative list of authors.

The organization of the book is appealing. It begins by providing chapters that have broad and uniform application including the major elements of cell structure and organization, the roles of genetics and immunology, and, finally, the biology of neoplasia. There then follow chapters devoted to the usual organ systems, but the addition of a separate section on connective tissue I found both helpful and informative. Finally, the concluding chapter deals with the topic of clinical pharmacology, and I compliment the authors for inclusion. This is probably one of medicine's most rapidly growing areas and Dr. Dollery does a professional job of characterizing its contribution to clinical medicine.

The book is well illustrated using appropriate feedback diagrams and electron micrographs to reinforce and expand the written work. Finally, the authors have held true to their theme and have not distracted the reader by providing clinical presentations that more appropriately fit in a textbook of medicine. In all, I found the book stimulating, readable and authoritative.

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in memoriam

California Medical Association

Auvil, Raymond George, Lone Pine. Died April 21, 1982, of cancer, aged 63. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Dr. Auvil was a member of the Inyo-Mono County Medical Society.

Balcer, Edwin A., Clearlake. Died May 13, 1982, of heart disease, aged 70. Graduate of Loyola University School of Medicine, Chicago, 1937. Licensed in California in 1957. Dr. Balcer was a member of the Alameda-Contra Costa Medical Association.

Beumer, Oliver C., San Leandro. Died September 17, 1982, aged 77. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1943. Licensed in California in 1943. Dr. Beumer was a retired member of the Alameda-Contra Costa Medical Association.

Brockbank, Mark J., Petaluma. Died August 17, 1982, in Petaluma of heart disease, aged 70. Graduate of Washington University School of Medicine, St. Louis, 1939. Licensed in California in 1946. Dr. Brockbank was a member of the Sonoma County Medical Association.

Chambers, Jack, Sacramento. Died June 2, 1982, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1936. Licensed in California in 1936. Dr. Chambers was a retired member of the Sacramento-El Dorado Medical Society.

Cox, George W., San Francisco. Died May 17, 1982, in Yountville, aged 97. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1912. Licensed in California in 1921. Dr. Cox was a retired member of the San Francisco Medical Society.

Cuneo, Joseph C., San Jose. Died April 6, 1982, aged 84. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1922. Licensed in California in 1924. Dr. Cuneo was a retired member of the Santa Clara County Medical Society.

Dole, Kenneth L., Pasadena. Died April 8, 1982, in Texas, aged 93. Graduate of Harvard Medical School, Boston, 1915. Licensed in California in 1919. Dr. Dole was a retired member of the Santa Clara County Medical Society.

Donoghue, Charles K., Long Beach. Died July 15, 1982, aged 61. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1958. Licensed in California in 1959. MD degree from California College of Medicine, 1962. Dr. Donoghue was a member of the Los Angeles County Medical Association.

Ehret, Edward E., San Clemente. Died June 27, 1982, aged 84. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr. Ehret was a retired member of the Los Angeles County Medical Association.

Hershey, Christian J., Rosemead. Died October 20, 1981, aged 82. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1926. Licensed in California in 1926. Dr. Hershey was a member of the Los Angeles County Medical Association.

Kaplan, Harry E., San Gabriel. Died June 7, 1982, in Bethesda, Maryland, aged 89. Graduate of Fordham University School of Medicine, New York, 1917. Licensed in California in 1921. Dr. Kaplan was a member of the Los Angeles County Medical Association.

Kutzmann, Adolph A., Los Angeles. Died January 21, 1982, aged 85. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Kutzmann was a retired member of the Los Angeles County Medical Association.

Idaho Medical Association

Gallivan, Edward L., Coeur d'Alene. Died March 29, 1982, aged 74. Graduate of St. Louis University School of Medicine, St. Louis, 1932. Licensed in Idaho in 1959. Dr. Gallivan was a retired member of the Kootenai-Benewah District Medical Society.

McWilliams, Charles R., Twin Falls. Died September 18, 1982, in Twin Falls of heart disease, aged 63. Graduate of State University of New York Downstate Medical Center, Brooklyn, 1943. Licensed in Idaho in 1950. Dr. McWilliams was a member of the South Central Idaho District Medical Society.

Starck, Jimmie C., Boise. Died September 25, 1982, in Boise of electrocution, aged 46. Graduate of Emory University School of Medicine, Atlanta, 1964. Licensed in Idaho in 1966. Dr. Starck was a member of the Ada County Medical Society.

Utah State Medical Association

Eddington, Elmo, Lehi. Died August 23, 1982, in Provo, aged 87. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1924. Licensed in Utah in 1931. Dr. Eddington was a member of the Utah County Medical Society.

Webster, James Weldon, Jr, Salt Lake City. Died August 13, 1982, in Salt Lake City, aged 49. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1961. Licensed in Utah in 1967. Dr. Webster was a member of the Salt Lake County Medical Society.

When mild to moderate pain is a side effect of "Fitness"

RUFEN®
(ibuprofen)

measures up... at a reasonable cost!

A Single-Entity Pain Reliever
As-Good-As or Better-Than Codeine Combinations

"...particularly effective in soft tissue disorders including sports injuries,"[1] Rufen stops pain at the site of injury and inflammation, not at the level of central perception. There is no dulled sensorium, no special need for warnings about driving or cautions about use of machinery. Your patient gets fast, effective pain relief...potent anti-inflammatory action...excellent tolerance...*plus* the exceptional economy that only Rufen offers. Next time one of your patients asks for pain relief, let Rufen show you how it measures up.

Boots Pharmaceuticals, Inc.
Shreveport, LA 71106
Pioneers in medicine for the family

See next page for brief summary of prescribing information.

Measure RUFEN® (ibuprofen) against "standard" mild to moderate pain

Dental pain and episiotomy pain are predictable, reproducible "standards" that make possible objective comparisons of effectiveness of different analgesic agents.

- Measured against 15, 30 and 60 mg doses of codeine phosphate in a double-blind study of 287 patients, 400-mg doses of ibuprofen proved "significantly better than codeine on almost all pain intensity, degree of relief and duration of analgesia parameters."[2]
- Measured against a propoxyphene-acetaminophen combination for pain relief after 3rd molar extractions, ibuprofen proved equally effective and caused fewer side effects. Ibuprofen was associated with faster recovery, evidenced by more rapid reduction of trismus and return to normal function.[3]
- Measured against post-episiotomy pain in 30 patients, "ibuprofen was effective in treating the swelling as well as pain...during the first and worst days. Therefore, it is not only the analgesic but also the anti-inflammatory effect of ibuprofen that are the beneficial factors..."[4]

Measure RUFEN® (ibuprofen) against any mild to moderate pain

RUFEN	Acetaminophen + codeine combinations
• single-entity, peripheral-acting analgesia	• combined drugs act partly through central opioid pathways
• powerful treatment of both pain and inflammation	• virtually no treatment of the inflammatory component
• better tolerated than aspirin	• combined side effects of two drugs—warning required about driving or operating machinery; possible respiratory depression with alcohol, tranquilizers, other common medications
• no narcotic risk, red tape, records	• narcotic precautions required
• matchless economy in a modern NSAID	

References:

1. Hart FD, Huskisson EC, Ansell BM in Hart FD (editor): Drug Treatment of the Rheumatic Diseases, 2nd Ed, Adis Press, Balgowlah, Australia, 1982, p. 30.
2. Rondeau PL, Yeung E, Nelson P: Canad Dent Assoc J 46:433-439, 1980
3. Selwyn P and Giles AD: Br Jrl of Clin Practice, Supplement 6, Safe and effective analgesia following dental surgery: A comparison of brufen and distalgesic. Pg 87-90. 1980.
4. Taina E: Curr Med Res Opinion, 7:423-428, 1981.

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And Rufen® Measures Up Best

RUFEN® (ibuprofen) Tablets

INDICATIONS AND USAGE: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in the long-term management of these diseases. Safety and effectiveness have not been established for Functional Class IV rheumatoid arthritis

Relief of mild to moderate pain. Treatment of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen, or with the syndrome of nasal polyps, angio-edema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (see WARNINGS).

WARNINGS: Anaphylactoid reactions have occurred in patients hypersensitive to aspirin (see CONTRAINDICATIONS). Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Peptic ulceration, perforation, or gastrointestinal bleeding can end fatally, however, an association has not been established. Rufen should be given under close supervision to patients with a history of upper gastrointestinal tract disease, and only after consulting the ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be attempted. If Rufen must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

PRECAUTIONS: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If developed, discontinue Rufen and administer an ophthalmologic examination.

Fluid retention and edema have been associated with Rufen, caution should be used in patients with a history of cardiac decompensation.

Rufen can inhibit platelet aggregation and prolong bleeding time. Use with caution in patients with intrinsic coagulation defects and those taking anticoagulants.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy, this therapy should be tapered slowly when adding Rufen.

DRUG INTERACTION: *Coumarin-type anticoagulants* The physician should be cautious when administering Rufen to patients on anticoagulants.

Aspirin. Concomitant use may decrease Rufen blood levels.

PREGNANCY AND NURSING MOTHERS: Rufen should not be taken during pregnancy nor by nursing mothers.

ADVERSE REACTIONS: Incidence greater than 1%. Gastrointestinal: The most frequent adverse reaction is gastrointestinal (4 to 16%). Includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence). Central Nervous System: dizziness*, headache, nervousness. Dermatologic: rash* (including maculopapular type), pruritus. Special Senses: tinnitus. Metabolic: decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS). *Incidence 3% to 9%.

Incidence less than 1 in 100. Gastrointestinal: gastric or duodenal ulcer with bleeding and/or perforation, hemorrhage, melena. Central Nervous System: depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma. Dermatologic: vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome and alopecia. *Special Senses:* hearing loss, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision) [see PRECAUTIONS]. Hematologic: neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs' positive), thrombocytopenia with or without purpura eosinophilia, decreases in hemoglobin and hematocrit. Cardiovascular: congestive heart failure in patients with marginal cardiac function, elevated blood pressure. Allergic: syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis, bronchospasms (see CONTRAINDICATIONS). Renal: acute renal failure in patients with preexisting significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria. Miscellaneous: dry eyes and mouth, gingival ulcers, rhinitis.

Causal relationship unknown. Gastrointestinal: pancreatitis. Central Nervous System: paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri. Dermatologic: toxic epidermal necrolysis, photoallergic skin reactions. Special Senses: conjunctivitis, diplopia, optic neuritis. Hematologic: bleeding episodes. Allergic: serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis. Endocrine: gynecomastia, hypoglycemia. Cardiovascular: arrhythmias (sinus tachycardia, bradycardia, and palpitations). Renal: renal papillary necrosis.

OVERDOSAGE: Acute overdosage, the stomach should be emptied. Rufen is acidic and excreted in the urine, alkaline diuresis may benefit.

DOSAGE AND ADMINISTRATION: Rheumatoid arthritis and osteoarthritis, including flareups of chronic disease: Suggested dosage 400 mg t.i.d. or q.i.d.

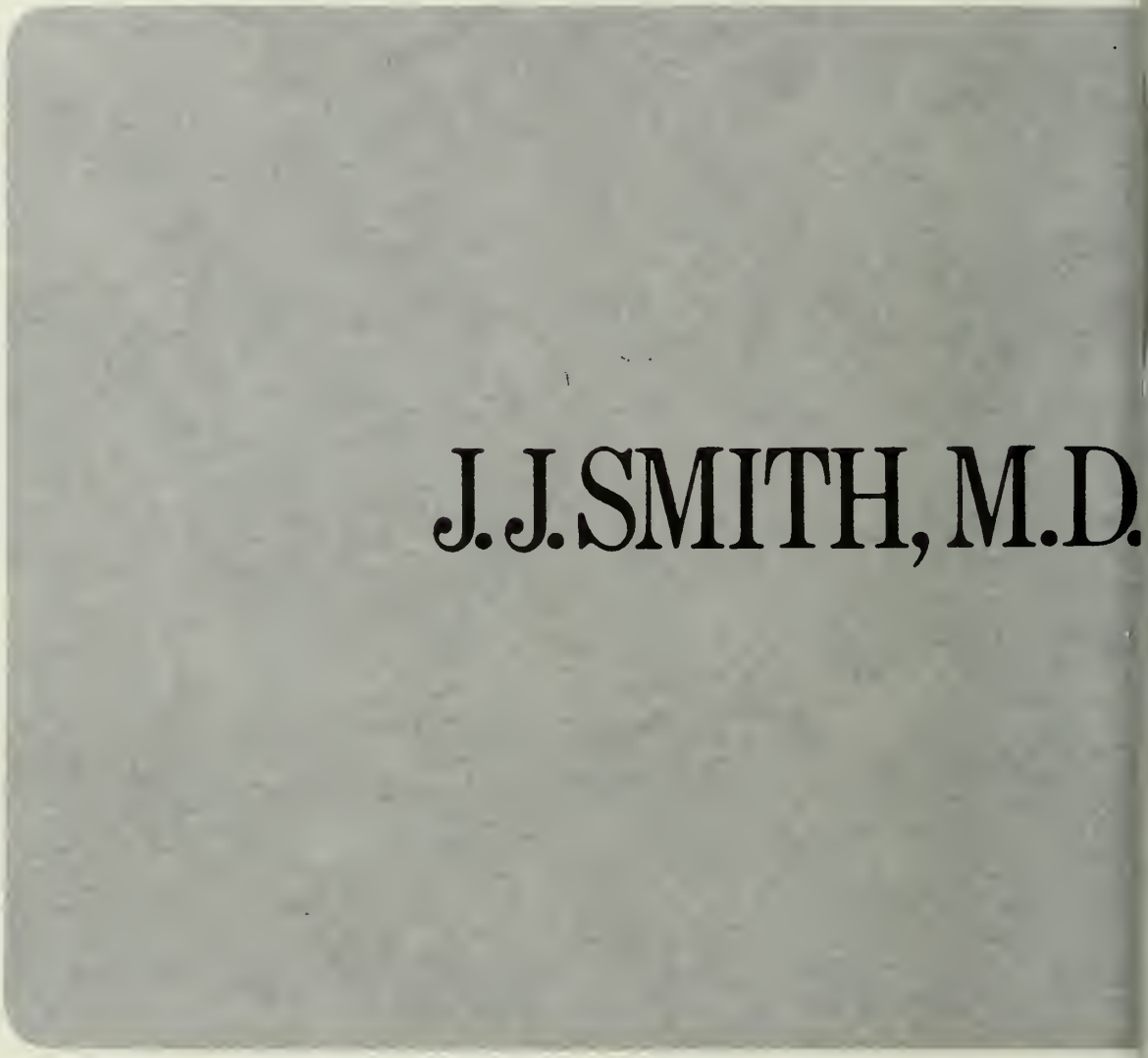
Dysmenorrhea: 400 mg every 4 hours as necessary

Mild to moderate pain. 400 mg every 4 to 6 hours as necessary for the relief of pain. *Do not exceed 2,400 mg per day*

CAUTION: Federal law prohibits dispensing without prescription.

SHE'S HERE FOR
YOUR EXPERT HELP

COUNSELING MAY HELP HER CONCERNS



*For moderate to severe vasomotor symptoms, atrophic vaginitis, surgical menopause, postmenopausal osteoporosis†

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 1.25 mg 2.5 mg

Counseling. It can help the menopausal woman through this difficult time. But counseli can't stop the moderate to severe vasomotor symptoms, reverse vaginal atrophy, or retard postmenopausal osteoporosis† the way PREMARIN tablets can.

PREMARIN. It may slow the progression of osteoporosis.† It controls her moderate to severe sweats and hot flushes. Relieves her discomfort. PREMARIN is a useful adjunct in your expert management of her menopausal symptoms.

PRESCRIBED WITH CA

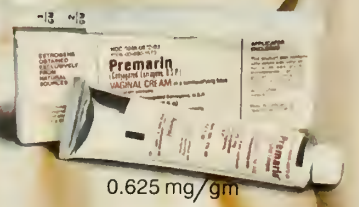
UT PREMARIN® HELPS HER CONDITION*

If her menopausal symptoms are limited to atrophic vaginitis, you're aware of the rapid, virtually complete relief PREMARIN Vaginal Cream provides. In the properly selected patient, it not only relieves the distressing symptoms of estrogen deficiency, such as dyspareunia, dryness and itching, but it rebuilds vaginal tissue.

PREMARIN Vaginal Cream. You know what it can do.

for atrophic vaginitis

PREMARIN®
(CONJUGATED ESTROGENS, U.S.P.) VAGINAL CREAM



0.625 mg/gm

Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis.

Please see following page for Brief Summary of Prescribing Information.

' PHYSICIANS WHO CARE.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.
Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.
2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY
The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease
9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.
PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).
CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).
WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.
Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolis or during periods of prolonged immobilization. Estrogens should not be used in persons w active thrombophlebitis, thromboembolic disorders, or in persons with a history of su disorders in association with estrogen use. They should be used with caution in patients w cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per da comparable to those used to treat cancer of the prostate and breast have been shown to increa the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. Wh doses of this size are used, any of the thromboembolic and thrombotic adverse effects should considered a clear risk.
Benign hepatic adenomas should be considered in estrogen users having abdominal pain a tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has be reported in women taking estrogen-containing oral contraceptives. Increased blood pressu may occur with use of estrogens in the menopause and blood pressure should be monitored w estrogen use. A worsening of glucose tolerance has been observed in patients on estroge containing oral contraceptives. For this reason, diabetic patients should be carefully observe Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone meta tases.
PRECAUTIONS: Physical examination and a complete medical and family history should taken prior to the initiation of any estrogen therapy with special reference to blood pressu breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a gene rule, estrogen should not be prescribed for longer than one year without another physi examination being performed. Conditions influenced by fluid retention such as asthm epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Cert patients may develop manifestations of excessive estrogenic stimulation, such as abnormal excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with increased incidence of mental depression. Patients with a history of depression should carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen us The pathologist should be advised of estrogen therapy when relevant specimens are submitte If jaundice develops in any patient receiving estrogen, the medication should be discontinu while the cause is investigated. Estrogens should be used with care in patients with impaired liv function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or young patients in whom bone growth is not complete.
The following changes may be expected with larger doses of estrogen:
a. Increased sulfobromophthalein retention
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increas norepinephrine-induced platelet aggregability
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyro hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin upta is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance
e. Decreased pregnanediol excretion
f. Reduced response to metyrapone test
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.
ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including o contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhe premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uteri fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervic secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nause vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which m persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhag eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to conta lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease weight, reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.
ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomot* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 m or more daily).
The lowest dose that will control symptoms should be chosen and medication should b discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals
2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failur Osteoporosis.
Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a re period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosag schedule is repeated. The number of courses of estrogen therapy necessary to produce bleedin may vary depending on the responsiveness of the endometrium.
If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cycli regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divide doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleedin occurs before this regimen is concluded, therapy is discontinued and may be resumed on th fifth day of bleeding.
Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward c downward according to response of the patient. For maintenance, adjust dosage to lowest lev that will provide effective control.
Osteoporosis (to retard progression)—1.25 mg daily, cyclically.
3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every fou hours for five doses, or 1.25 mg every four hours for five days.
4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three time daily.
Inoperable progressing breast cancer in appropriately selected men and postmenopausa women—10 mg three times daily for a period of at least three months.
Patients with an intact uterus should be monitored for signs of endometrial cancer an appropriate measures taken to rule out malignancy in the event of persistent or recurrin abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream
Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.
The lowest dose that will control symptoms should be chosen and medication should b discontinued as promptly as possible.
Administration should be cyclic (e.g., three weeks on and one week off).
Attempts to discontinue or taper medication should be made at three to six month intervals.
Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of th condition.
Treated patients with an intact uterus should be monitored closely for signs of endometria cancer and appropriate diagnostic measures should be taken to rule out malignancy in the even of persistent or recurring abnormal vaginal bleeding.
HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.
PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol sodium lauryl sulfate, glycerin, and mineral oil.)
Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.
Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. 7814/882

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New York, N.Y. 10017

(Continued from Page 34)

day. Contact: Dr. Charles Buchwald, Downstate Med. Ctr., 450 Clarkson Ave.-Box 129, Brooklyn, NY 11203. (212) 270-3150.

November 19-21—**Pain Management.** UCLA. Friday-Sunday. 12 hrs. $180.

November 20-27—**3 for 1: Proctology; Psychiatry; Principles.** See Psychiatry, November 20-27.

November 21-24—**Pacific Coast College Health Association—Annual Meeting.** PCCHA and San Diego State Univ., Student Health Services, at Hyatt Islandia, San Diego. Sunday-Wednesday. 14 hrs. $40, members; $50, nonmembers. Contact: David Bearman, MD, Dir., Student Health Services, San Diego State Univ., San Diego 92182. (714) 265-5281.

December 3—**Stroke: An Integrated Approach.** Daniel Freeman Memorial Hospital, Inglewood. Friday. 7 hrs. $90. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., Daniel Freeman Mem. Hosp., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

December 4-5—**Emerging Frontiers in Medicine: An Update for the Practicing Physician.** Cypress Foundation and UCSF at Hyatt Del Monte, Monterey. Saturday-Sunday. 10 hrs. $150. Contact: Cypress Fndn., Box 80308, Salinas 93912. (408) 455-1833.

December 30-31—**Second Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Thursday-Friday. Contact: Arlene M. Ellis, Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5165.

January 15-23—**Intensive Course in Geriatric Medicine.** American College of Physicians at Santa Monica. 9 days. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104. (215) 243-1200.

January 17-18—**International Symposium: The Psychobiology of Alcoholism.** UCLA at Beverly Hilton, Beverly Hills. Monday-Tuesday. 13 hrs. $225.

January 21—**Medical Consequences of Nuclear Weapons and Nuclear War.** UCD at Sacramento Convention Center, Sacramento. Friday.

January 22—**Rape and Domestic Violence.** UCLA. Saturday.

January 24-28—**Primary Care: Current Management of Common Office Problems.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Tuesday. 33 hrs. $300.

February 2-4—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 23 hrs. Contact: Edith S. Bookstein, 7810 Lookout Dr., La Jolla 92037. (714) 454-3212.

February 5—**Alcohol and Drug Problems in the Later Years.** UCLA. Saturday. 5½ hrs. $100.

February 7-11—**Nutritional Aspects of Obesity Management.** American Society of Bariatric Physicians at Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. $295, members; $325, nonmembers. Contact: ASBP, 5200 S. Quebec, Suite 300, Englewood, CO 80111. (303) 779-4833.

February 7-12—**UCI Family Practice Refresher Course.** UCI at Marriott, Newport Beach. Monday-Saturday. 50-56 hrs. $525. Contact: UCI Extension, P.O. Box AZ, Irvine 92714. (714) 833-5414.

February 9-April 13—**Biofeedback Review Course.** UCLA. Wednesday evenings. 30 hrs.

February 10-12—**Practical Cardiology for Family Physicians, 1983.** American College of Cardiology at Eisenhower Medical Center, Rancho Mirage. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

February 11—**Geriatric Medicine, Symposium II—"Special Health Concerns of the Elderly."** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Marsha Vacca, Geriatrics Coordinator, Sutter Gen. Hosp., 28 and L Sts., Sacramento 95816. (916) 454-2222, ext. 1233.

February 12-19—**Updates in Acute Medicine: An Epic Medical Expedition.** American Inst. of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

February 14-25—**Intensive Residency in Occupational Medicine, II.** UCSF at Golden Gateway Holiday Inn, San Francisco. Two weeks. 80 hrs.

February 20-24—**Winter Sports Injuries.** UCD at Hyatt, Lake Tahoe. Sunday-Thursday. 15 hrs.

February 21-25—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $365.

March 3-6—**Critical Care Medicine—21st Annual Symposium.** USC at MGM Grand, Las Vegas. Thursday-Sunday. 28 hrs.

March 5-6; 19-20—**San Francisco Academy of Hypnosis—Annual Workshop.** Letterman Army Medical Center, San Francisco. Two weekends. 28 hrs. $275. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco 94114.

March 5-12—**Future Directions and Update on Family Practice.** Univ. of Washington School of Medicine at Sheraton Royal Waikiloa, Kona. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

March 9-11—**33rd Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Nancy Drungilas, Office of Cont. Ed., Mt. Zion Hosp., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

March 9-11—**American Society for Clinical Pharmacology and Therapeutics.** Town and Country Hotel, San Diego. Wednesday-Friday. Contact: ASCPT, 1718 Gallagher Rd., Norristown, PA 19401.

March 10-13—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $250.

March 11-16—**California Medical Association—112th Annual Session.** Bonaventure Hotel, Los Angeles. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 12—**Total Parenteral Nutrition.** UCLA. Saturday.

March 18—**Nora Eccles Harrison Diabetes and Nutrition Update.** UCD at Hilton, San Francisco. Friday. 6 hrs.

March 19-26—**Advances in Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

March 26—**Alcoholism and Its Treatment: 1983.** UCD at Sacramento Inn, Sacramento. Saturday. 7 hrs.

ALASKA

November 19-20—**Gastroenterology Conference.** Anchorage. Friday-Saturday. Providence Hospital. 14 hours Category 1 credit. Fee: $65. For further information, fees, credit and program contact: Judy Kyle, Education and Training Department, Providence Hospital, 3200 Providence Drive—Pouch 6604, Anchorage, AK 99502. (907) 276-4511, Ext. 1005.

IDAHO

January 15-22—**Updates in Pediatrics: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 19-26—**Updates in Acute Medicine: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American

(Continued on Page 49)

THE WESTERN JOURNAL OF MEDICINE
INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 731 Market Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976*, transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed double-spaced throughout (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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(Continued from Page 36)

PHYSICIANS WANTED

CHIEF OF MEDICINE needed at VA Medical Center, Livermore, California. Board certification in Internal Medicine is required. Experience in Rheumatology and/or Infectious Diseases is preferred and previous administrative experience is also desirable. Malpractice insurance not needed. Position available at present. Salary dependent upon experience and qualifications. Contact: Bruce M. Titus, MD, Acting Chief, Medical Service, VA Medical Center, Livermore, CA 94550. Tel: (415) 447-2560, Ext. 6200.

DIAGNOSTIC RADIOLOGIST—with minimum 1 year fellowship neuroradiology to perform general diagnosis with neuro emphasis. Group with office and hospital practice, medium size Pacific Northwest city. Salary negotiable. CV to reply Box 6320, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UNIVERSITY HOSPITAL; AMBULATORY PHYSICIAN WANTED. Board eligible/certified in internal medicine. Long-term commitment desired. Send CV to C. Kapsner, MD, University of New Mexico, Albuquerque, NM 87131.

ASSOCIATE WANTED

BUSY THORACIC SURGICAL PRACTICE in Southern California seeks ABTS certified individual as associate. Excellent opportunity for partnership/acquisition of practice in a reasonable time frame. Applicants should send a complete curriculum vitae with at least three references to Box 6319, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OHIO—ABAI certified, 68 year old, tremendous practice, large city, three medical school affiliations, and director of hospital Allergy Clinic, seeks associate for partnership, etc. Must be ABAI certified or eligible. Send curriculum vitae and other pertinent information to Box 6322, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

POSITIONS AVAILABLE

GP AS A PARTNER TO INTERNIST. Can buy into existing practice oriented towards treatment of diabetes. San Diego County, California. Reply to P.O. Box 4137, Irvine, CA 92716.

DUE TO DEATH AND RETIREMENT, our clinic is now organized as an expense sharing association and has available office space for OB/Gyn and Internal Medicine. The only OB/Gyn specialist in the community retired over a year ago and there is a demand for such a specialist. Medical Building Associates (nee Taylor Richardson Clinic) P.O. Box 369, Ellensburg, WA 98926.

LOCUM TENENS WORK WANTED

GENERAL PRACTITIONER, 37, available California or Washington. Please write J. D. Rienstra, MD, 859 6th St., B-201, Bremerton, WA 98310.

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. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena Bl., Alameda, CA 94501. (415) 521-4110.**

FOR SALE

HIGHLY VISIBLE 1,095 sq. ft. medical-dental office building 4 blocks from O'Connor Hospital in San Jose opposite Payless Drug Store of Valley Fair Shopping Center. Zoned professional. 5 off-street parking spaces with turn-around. Dental office for past 19 years. $175,000. Walter Drozdiak, DDS, 2337 Forest Avenue, San Jose, CA 95128. (408) 241-4480, Eves. (408) 264-9278.

SITUATIONS WANTED

BOARD CERTIFIED INTERNIST with subspecialty training in Endocrinology and Metabolism seeks practice opportunity in Southern California. Reply Box 6316, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

CALIFORNIA TRAINED INTERNIST—Anxious to return to the Southern West Coast. Currently assistant professor at top midwest university. Box 6297, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST-ENDOCRINOLOGIST, 33, ABIM, University trained with interest in Diabetes. seeks private practice in Northern California, preferable Bay Area. Available June 1983. Reply Box 6321, Western Journal of Medicine, 731 Market St., San Francisco 94103.

GENERAL INTERNIST, 32, ABIM, University trained, with extensive Primary Care experience, seeks clinic or hospital-based Ambulatory Care Position. Reply to Box 6323, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SURGICAL MENTOR WANTED by physician. I wish to arrange a part-time preceptorship under an experienced surgeon, assisting you at emergency and/or elective surgery at your hospital. I am a general practitioner (California license) preparing for practice in a remote hospital overseas where I will be the only physician available for surgical emergencies. Please contact: Richard Solomon, MD, 3920 McClure St., Oakland, CA 94609. (415) 444-5676.

PRIMARY CARE INTERNIST seeks position. Will consider clinics, hospitals, groups, partnership, occupational. Compensation negotiable. Reply AT, 132 Midland Place, Newark NJ 07106; or call (201) 373-2240.

CANADIAN INTERNIST-GASTROENTEROLOGIST, 30, seeks position on West Coast or Pacific Northwest. Trained in Gastroscopy, Colonoscopy, Polypectomy, ERCP, Manometry. Research experience. Private practice preferred. Box 6324, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

UROLOGIST. 14 years solo practice same location. Boards, FACS. Desire relocation to S.W., W., N.W. All practice arrangement considered. CV on request. Box 6326, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FOR LEASE OR RENT

FOR LEASE: 2,500 sq. ft. physicians office in Bullhead City, Arizona. Continuously occupied by physicians and surgeons since 1968. Bullhead will have new hospital (Baptist) in ±12 months and is ready for additional physicians. Enjoy Lake Mohave (5 miles). Colorado River (¼ mile), and casino gambling in a semi-rural setting. Lease negotiable; unquestionably less than comparable facility in urban location. (602) 754-2515 or (602) 758-7868.

SAN BRUNO, CALIFORNIA (just South of San Francisco). Rental space avail. in new full service medical building. Great opportunity for Int. Med., GP, Derm., Neuro., Ortho., Gen. Surg., Ped., Ob/Gyn., Psych., Ophtho., and other medical and surgical sub-specialities. Nearby hospital privileges available. Contact Stan Nudleman, MD, 1001 Sneath Lane, #300, San Bruno, CA 94066, (415) 583-5352.

MARIN MED. OFFICE FOR RENT—Med. Dental Bldg., San Anselmo, California. Near hospital, transportation, shopping. Parking. (415) 453-8948.

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CENTRAL CALIFORNIA COAST—New offices in group setting. Now you can have the best of both worlds. Practice in a dynamic med/dent group or solo. In two growing areas in one of the best locations in the nation, near Monterey Peninsula. Also much new and used medical equipment for sale. Call now for information on these unusual opportunities. (408) 659-4828.

MEDICAL PRACTICES FOR SALE

GENERAL PRACTICE—Long established (42 years). Antioch, California. 50,000 population. Easy terms—negotiable. Call evenings 7-10 p.m. Phone: (415) 757-5205.

FAMILY PRACTICE—Tacoma, Washington. Heart of Puget Sound area, 25 mi. South of Seattle. Unique opportunity—especially suited for outdoors-oriented family type. Available immediately. Well established. $250,000/yr potential. Call (206) 232-5665 anytime and leave message for information package.

OB/GYN PRACTICE. Aspen, Colorado. Gross over $200,000, write for further information. Box 11626, Aspen, CO 81611.

PRESCOTT, ARIZONA: General Internal Medicine practice for sale. A mile up in the pines of sunny central mountains 90 minutes from Phoenix. Town of 25,000 surrounded by beautiful National Forest land. Delightful summers; mild winters. Four day week solo practice grossed over $165,000 last year. Completely furnished office in medical building across from hospital. Also, beautiful hilltop passive solar house with tennis court for sale. Leaving Arizona for East. Available immediately, will introduce. (602) 445-5785. First time offered.

UNOPPOSED ADULT ONCOLOGY-HEMAT.: Intentionally limited. Good potential for full time. Possible lease or partnership in multispecialty group. California license. Northern California wine, timber country. H. W. Gordon, MD, 198 Doolin Dr., Ukiah, CA 95482.

GYN PRACTICE SAN FRANCISCO. Well established, high gross. Adjacent teaching hospital. OB can be readily developed. Exceptional opportunity for well-qualified individual. Send CV with cover letter. Box 6327, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DERMATOLOGY PRACTICE, La Mirada Mall, California. Call (213) 473-8666. Nets $40,000/year. Fully equipped. $40,000 price or best offer. Must sell due to personal difficulties unrelated to medical practice.

CALIFORNIA AND DENVER. HIGH INCOME. Family Practices for sale in desirable living areas. Others: OB/GYN, Internal, Psychiatry, Orthopedic, Surgery. Contact Professional Practices Opportunities, Mary Bradshaw, 21 Altamount Dr., Orinda, CA 94563. (415) 376-0762.

EQUIPMENT NEEDED

X-RAY UNIT PLUS ACCESSORIES. 300 MA—125 KV minimum. Also interested in other office equipment. Call (206) 535-1886. Will arrange for transportation.

PRACTICE FOR SALE

PRESCOTT, ARIZONA: General Internal Medicine practice for sale. A mile up in the pines of sunny central mountains 90 minutes from Phoenix. Town of 25,000 surrounded by beautiful National Forest land. Delightful summers; mild winters. Four day week solo practice grossed over $165,000 last year. Completely furnished office in medical building across from hospital. Also, beautiful hilltop passive solar house with tennis court for sale. Leaving Arizona for East. Available immediately, will introduce. (602) 445-5785. First time offered.

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(Continued from Page 45)

Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

March 19-26—**Updates in Trauma: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

See also Washington Listings: February 5-12, 12-19, 14-18, 19-26, February 26-March 5, 5-12.

MONTANA

January 8-15—**Updates in Acute Medicine: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Saturday-Saturday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 8-15—**Updates in Trauma: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Tuesday-Tuesday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

March 26-April 2—**Updates in Pediatrics: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Saturday-Saturday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed.

(Continued on Page 53)

Family Practice Internal Medicine Obstetrics/Gynecology

Family Health Program, one of the nation's leading health maintenance organizations, has openings in **Family Practice**, **Internal Medicine** and **Obstetrics/Gynecology** on its Utah medical staff.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ACHIEVING PATIENT COMPLIANCE—The Psychology of the Medical Practitioner's Role—M. Robin DiMatteo, PhD, Associate Professor of Psychology, University of California, Riverside; and D. Dante DiNicola, BS, fourth year medical student, University of Los Angeles, School of Medicine. Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523, 1982. 333 pages, $35.00 (hardcover), $12.95 (softcover).

AFRICAN LITERATURE: A Critical View—David Cook, Professor of English, University of Ilorin, Nigeria. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1977. 240 pages, $10.95 (softbound).

BASIC & CLINICAL IMMUNOLOGY—Fourth Edition—Daniel P. Stites, MD, and John D. Stobo, MD, University of California, San Francisco; H. Hugh Fudenberg, MD, Medical University of South Carolina, Charleston; and J. Vivian Wells, MD, FRACP, FRCPA, Royal North Shore Hospital, Sydney. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 775 pages, $22.00.

BASIC NEUROLOGY—John Gilroy, MD, Professor and Chairman, Department of Neurology, Wayne State University; Chief, Department of Neurology, Harper-Grace Hospitals and Detroit Receiving Hospital, Detroit; and Patti L. Holliday, MD, Resident in Neurology, Wayne State University. Macmillan Publishing Co., Inc, 866 Third Ave., New York, NY 10022, 1982. 373 pages, $18.95.

BETTER HEALTH WITH FEWER PILLS—Louis Shattuck Baer, MD, Burlingame, California. The Westminister Press, 925 Chestnut Street, Philadelphia, PA 19107, 1982. 168 pages, $5.95 (paperback).

CARDIOLOGY FOR THE HOUSE OFFICER—Joel W. Heger, MD, Pasadena, California; James T. Niemann, MD; Keith G. Boman, MD, and J. Michael Criley, MD, Harbor-UCLA Medical Center, Torrance, California. The Williams & Wilkins Company, 428 E. Preston St., Baltimore, MD 21202, 1982. 288 pages, $9.95 (softbound).

CONGENITAL DISLOCATION OF THE HIP—Edited by Mihran O. Tachdjian, MD, Professor of Orthopedic Surgery, Northwestern University Medical School, Chicago. Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1982. 798 pages, $89.00.

CORRELATIVE NEUROANATOMY & FUNCTIONAL NEUROLOGY—18th Edition—Joseph G. Chusid, MD, Professor of Neurology, New York Medical College; Director of Department of Neurology, St. Vincent's Hospital and Medical Center, New York City. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 476 pages, $15.00.

CURRENT OBSTETRIC & GYNECOLOGIC DIAGNOSIS & TREATMENT—Fourth Edition—Edited by Ralph C. Benson, MD, Professor of Obstetrics & Gynecology and Emeritus Chairman, Department of Obstetrics & Gynecology, The Oregon Health Sciences University, Portland; with associate authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 1,038 pages, $25.00.

DISPOSITION OF TOXIC DRUGS AND CHEMICALS IN MAN—Second Edition—Randall C. Baselt, PhD. Biomedical Publications, P.O. Box 495, Davis, CA 95617, 1982. 795 pages, $49.50.

GUIDE TO DIAGNOSTIC IMAGING—Volume I: THE LIVER & SPLEEN—Alexander Kovac, MD, Chief, Radiology Service, Veterans Administration Medical Center, Phoenix; Adjunct Assistant Professor of Radiology, University of Arizona College of Medicine, Tucson. Medical Examination Publishing Co., Inc., 3003 New Hyde Park Road, New Hyde Park, New York 11040, 1982. 229 pages, $33.00 (hardcover).

HANDBOOK OF HEART TERMS—The National Heart, Lung & Blood Institute. Enslow Publishers, Bloy Street and Ramsey Ave., Box 777, Hillside, NJ 07205, 1982. 63 pages, $4.95.

HAND PAIN AND IMPAIRMENT—Edition 3—Rene Cailliet, MD, Professor and Chairman, Department of Rehabilitative Medicine, University of Southern California School of Medicine, Los Angeles, California. F. A. Davis Company, 1915 Arch Street, Philadelphia, PA 19103, 1982. 232 pages, $11.95.

INTRODUCTION TO CLINICAL RADIOLOGY—Wallace T. Miller, MD, Professor and Vice Chairman, Department of Radiology, University of Pennsylvania School of Medicine, Philadelphia. Macmillan Publishing Co., Inc., 866 Third Ave., New York, NY 10022, 1982. 291 pages, $24.50.

LUNG DEVELOPMENT: BIOLOGICAL AND CLINICAL PERSPECTIVES—Volume II: NEONATAL RESPIRATORY DISTRESS—Edited by Philip M. Farrell, Department of Pediatrics, University of Wisconsin Clinical Sciences Center, Madison. Academic Press, Inc., Publishers, 111 Fifth Ave., New York, NY 10003, 1982. 307 pages, $37.50.

MALIGNANT DISEASE OF THE VULVA—Stanley Way, FRCS(Eng), FRCOG; assisted by David Guthrie, MB, BS, MRCOG, and Peter Philips, BSc, PhD. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 83 pages, $24.75.

MNEMONICS, RHETORIC AND POETICS FOR MEDICS—Robert L. Bloomfield, MD, and E. Ted Chandler, MD, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. Harbinger Press, Box 17201, Winston-Salem, NC 27106, 1982. 222 pages, $9.50 (softbound).

MODERN METHODS IN PHARMACOLOGY—Volume 1—Editors: Sydney Spector, Roche Institute of Molecular Biology, Nutley, NJ; and Nathan Back, State University of New York, Buffalo. Alan R. Liss, Inc., 150 Fifth Ave., New York, NY 10011, 1982. 93 pages, $14.00.

OPEN HEART: A First Person Account—David M. Heath. R & E Publishers, P.O. Box 8, Saratoga, CA 95071, 1982. 127 pages, $9.95 plus $1.50 shipping (special pre-publication price of $7.95 plus $1.00 shipping).

OPERATIVE HAND SURGERY—Volumes 1 and 2—Edited by David P. Green, MD, Clinical Professor of Orthopaedics; Former Chief, Hand Surgery Service, University of Texas Health Science Center at San Antonio. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 1,754 pages, in 2 volumes, $170.00.

ORTHOPEDIC REHABILITATION—Edited by Vernon L. Nickel, MD, Professor of Surgery/Orthopedics and Rehabilitation, University of California, San Diego, School of Medicine. Churchill Livingstone Inc., 19 West 44th Street, New York, NY 10036, 1982. 594 pages, $65.00.

OUTLINE GUIDE TO ANTIMICROBIAL THERAPY—John E. McGowan, Jr, MD, Professor of Medicine and Professor of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta. Medical Economics Books, Box 157, Florence, KY 41042, 1982. 175 pages, $13.95* (plus handling charge). *Prices are subject to change without notice.

PATHOLOGY OF GRANULOMAS AND NEOPLASMS OF THE NOSE AND PARANASAL SINUSES—Imrich Friedmann, MD, DSc, FRCS, FRCPath, DCP, and the late Denis A. Osborn, MD, FRCPath. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 306 pages, $65.00.

PATIENT CARE FLOWCHART MANUAL—Third Edition—Medical Economics Books, Box 157, Florence, KY 41042, 1982. 590 pages, $39.95* (plus $1.50 handling charge). *Prices are subject to change without notice.

PHLEBOGRAPHY OF THE LOWER LIMB—M. Lea Thomas, MA, MB, BChir, FRCP, FRCR. Churchill Livingstone, Inc., 19 West 44th St., New York, NY 10036, 1982. 220 pages, $39.00.

PHYSICIANS' GUIDE TO OCULOSYSTEMIC DISEASES—Ophthalmoscopic Physical Diagnosis—William V. Delaney, Jr, MD, Department of Ophthalmology, Upstate Medical Center, State University of New York, Syracuse. Medical Economics Books, Box 157, Florence, KY 41042, 1982. 499 pages, $49,50* (plus $1.50 handling charge). *Prices are subject to change without notice.

PRINCIPLES OF CLINICAL ELECTROCARDIOGRAPHY—11th Edition—Mervin J. Goldman, MD, Clinical Professor of Medicine, University of California, San Francisco, School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1982. 438 pages, $15.00.

QUALITY CONTROL—Volume 4 in METHODS IN HEMATOLOGY—Edited by I. Cavill, PhD, MRCPath, Senior Lecturer in Haematology, Welsh National School of Medicine, Cardiff, Wales. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 191 pages, $35.00.

RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA—Number Fourteen—Edited by R. S. Atkinson, MB, BChir, and C. Langton Hewer, MB, BS, MRCP. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 182 pages, $29.00 (softbound).

RECENT ADVANCES IN COMMUNITY MEDICINE—Number 2—Edited by Alwyn Smith, PhD, FRCP, FFCM, FRCGP. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 212 pages, $35.00.

RHEUMATOLOGY IN GENERAL PRACTICE—Volume 3 in Library of General Practice—Michael Rogers, MB, ChB, DObst, RCOG, and Norman Williams, MA, MRCP. Churchill Livingstone Inc., 19 West 44th St., New York, NY 10036, 1982. 266 pages, $18.75 (softbound).

SCHNEIERSON'S ATLAS OF DIAGNOSTIC MICROBIOLOGY—Eighth Edition—Edited by Edward J. Bottone, PhD, Director, Department of Microbiology, Mount Sinai Hospital, New York; Roland Girolami, PhD, and John M. Stamm, MSc SM(AAM), Abbott Laboratories, North Chicago. Abbott Laboratories, Professional Relations D-383, Abbott Park, North Chicago, IL 60064, 1982. 80 pages, with 200 color plates (No. 97-1532) available for $2.75 per copy, prepaid from Abbott Laboratories.

TYPES OF MEDICAL PRACTICE: Making Your Choice—Norton Mockridge. Medical Economics Books, Box 157, Florence, KY 41042. 272 pages, $21.50* (plus $1.50 handling change). *Price is subject to change.

1983 USP DI—Volume I: DRUG INFORMATION FOR THE HEALTH CARE PROVIDER—Volume II: ADVICE FOR THE PATIENT—The United States Pharmacopeial Convention, Inc. USP DI, Distribution Department, 12601 Twinbrook Parkway, Rockville, MD 20852, 1982. Volume 1, 982 pages; Volume II, 793 pages; $37.95 for the 2-volume set; $17.95 for Volume II only; $9.00 for updates through December 1983.

THE WHYS AND WHEREFORES OF CORPORATE PRACTICE—Fourth Edition—Sheldon H. Gorlick, JD. Medical Economics Books, Box 157, Florence, KY 41042, 1982. 156 pages, $19.95* (plus $1.50 handling charge). *Prices are subject to change without notice.

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY—14th Edition—Robert Berkow, MD, Editor-in-Chief; Editorial Board: Donald C. Bondy, MD; Philip K. Bondy, MD; Alvan R. Feinstein, MD; Alfred P. Fishman, MD; Robert A. Hoekelman, MD; John W. Ormsby, MD; Robert G. Petersdorf, MD; G. Victor Rossi, PhD; George E. Schreiner, MD, and John H. Talbott, MD. Merck Sharp & Dohme Research Laboratories, A Division of Merck & Co., Inc., Rahway, NJ 07065, 1982. 2,578 pages, $19.75 (Regular Hard-Cover Binding). Also available in two-volume set, soft-cover format: Vol. I—General Medicine; Vol. II—Gynecology, Obstetrics, Pediatrics, and Genetics. Volume I is $11.95 and Volume II is $6.95. (Books may be ordered through medical book dealers or directly from Merck & Co., Inc., Publications Department, Box 2000, Rahway, NJ 07065.

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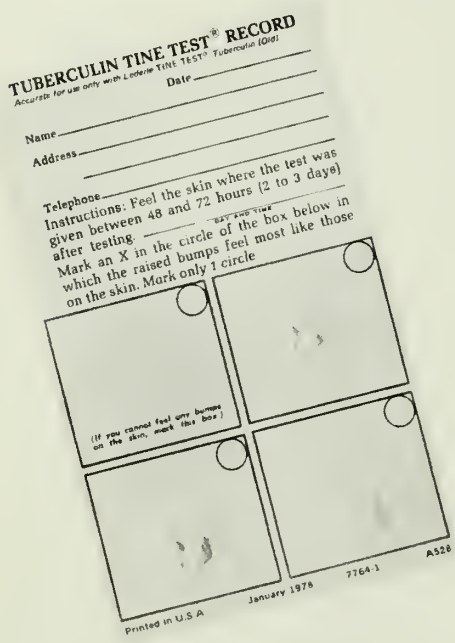

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INFORMATION/ REGISTRATION: (801) 581-3581
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University Medical Center
Salt Lake City, UT 84132

(Continued from Page 49)

Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

January 28-29—**Physicians Conference on Alcoholism & Chemical Dependence.** Albuquerque. Friday-Saturday. Marriott Hotel. 12 credit hours. Contact: Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7621 (Rod Waller, CARE UNIT) or (505) 842-7000 (Martin Conway, MD).

February 14-17—**Taos Medical Symposium.** Taos. Monday-Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II, MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

February 27-March 3—**New Mexico Metabolism Symposium.** Taos. Sunday-Thursday. Tennis Ranch of Taos. 15 credit hours. Contact: Martin Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

February 28-March 4—**Purgatory Ski Symposium.** Durango, Colorado. Monday-Friday. Tamaron Lodge. 20 credit hours, also AAFP. Contact: Gwenn Robinson,MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 14-18—**Annual Family Practice Review.** Portland. Monday-Friday. Red Lion Motor Inn at Lloyd Center. For information contact: OHSU-CME.

EMERGENCY MEDICINE

February 11-12—**Poisonings & Toxicologic Emergencies.** Portland. Friday-Saturday. Red Lion Motor Inn at Lloyd Center. For information contact: Veronica Story, Oregon ACEP, 5210 SW Corbett, Portland, OR 97201. (503) 226-1555.

PATHOLOGY

March 10-11—**Workshop in Dermatopathology.** Portland. Thursday-Friday. Oregon Medical Association, 5210 SW Corbett. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

March 4-5—**Complex and Controversial Issues in Multiple System Trauma.** Portland. Friday-Saturday. Red Lion Inn Downtown. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

November 18-19—**Symposium on Critical Care Medicine.** Portland. Thursday-Friday. Red Lion Motor Inn at Jantzen Beach. For information contact: OHSU-CME.

December 2—**New Approaches in Hypertension.** Portland. Thursday. Red Lion Motor Inn at Lloyd Center. For information contact: OHSU-CME.

December 3—**Update in Infectious Diseases.** Portland. Friday. Red Lion Motor Inn at Lloyd Center. For information contact: OHSU-CME.

(Continued on Page 55)

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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(Continued from Page 53)

April 13-15—**Sommer Memorial Lectures/Alumni Association Scientific Sessions.** Portland. Wednesday-Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

May 20-21—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn-Lincoln St. For information contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Every Friday—7:30-8:30 a.m. Contact: Thomas Schwenk, MD, (801) 350-4111.

CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

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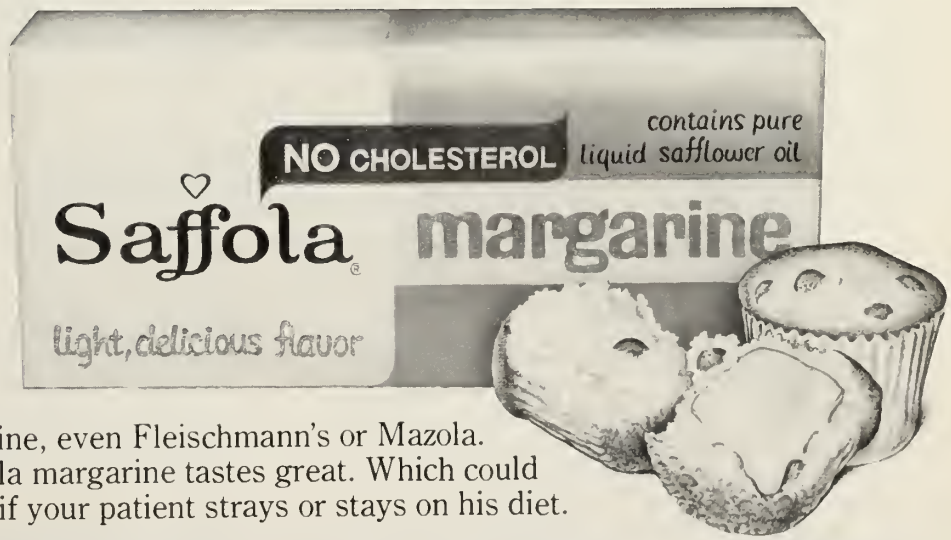

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Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

November 15—**Sudden Infant Death Syndrome (SIDS) Conference** (Sponsors: University of Utah/Utah State Dept. of Health). Salt Lake City. Monday. Snowbird. Credit: To be announced. Fee: $25. Contact: Trisha Keller (801) 533-4232.

November 19—**Common Nerve Entrapments** (Sponsor: McKay-Dee Hospital Center). Ogden. Friday. 1 hr. No fee. Contact: (801) 627-3202.

December 3—**Applications of Mass Spectrometry to Quantitative and Structural Analysis in Biochemistry/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

January 7—**Effect of Surgery for Variceal Hemorrhage on Hepatic Blood Flow and Cerebral Function/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

January 21—**Treatment of Upper Extremity Pain Syndromes** (Sponsor: McKay-Dee Hospital Center). Ogden. Friday. 1 hr. No fee. Contact: (801) 627-3202.

January 21-23—**7th Annual U of U Seminar on Sexual Function/Dysfunction** (Sponsor: University of Utah). Park City.

Friday-Sunday. 19 hrs. Fee: $200. Contact: Claire Turner (801) 581-5809.

January 26-February 3—**Air Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. Credit and fee to be announced. Contact: Dennis C. Brimhall, MD (801) 581-2682.

January 31-February 4—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. $350. Contact: John Matsen, MD (801) 581-5514.

February 4—**Host Functions Essential for Bacteriophage Growth/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

February 14-17—**12th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 28 hrs. $280. Contact: Linda Twitchell (801) 581-8633.

February 18-22—**28th Annual Postgraduate Course in Anesthesiology** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hilton Hotel. 17 hrs. Fee to be announced. Contact: Ted Stanley, MD (801) 581-7647.

February 19-22—**24th Annual Ob/GYN Postgrad Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 23-26—**Perinatal Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 25—**Special Problems in Stroke Recovery** (Sponsor: McKay-Dee Hospital Center). Ogden. Thursday. 1 hr. No fee. Contact: (801) 627-3202.

March 4—**Blood and Marrow Neutrophil Kinetics During Group B Streptococcal Sepsis/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

April 1—**Connective Tissue Genes: Their Structure and Expression in Cells of the Arterial Wall/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

April 5-8—**The 5th Annual RMCOEH Occupational and Environmental Health Conference: Reproduction: The New Frontier in Occupational and Environmental Health Research** (Sponsor: University of Utah/RMCOEH). Park City. Tuesday-Friday. Prospector Square. Credit and fee to be announced. Contact: Ms. K. Blosch (801) 581-5710.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

November 19—**Neuroophthalmology Seminar.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

(Continued on Page 58)

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(Continued from Page 56)

November 19-20—**(ALASKA) Gastroenterology Conference.** Anchorage, Alaska. Friday-Saturday. Providence Hospital. 14 hours Category 1 credit. Fee: $65. Contact: Judy Kyle, Education and Training Department, Providence Hospital, Pouch 6604, Anchorage, AK 99502. (907) 276-4511 ext. 1005.

November 20-27—**(HAWAII) 3 For 1: Proctology, Psychiatry, Principles.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

November 20-27—**(HAWAII) Financial Planning.** Kona. Saturday-Saturday. Sheraton Waikoloa. Contact: U/W.

December 2-3—**Surgical Aspects of Lung Disease.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

December 3—**Practical Pediatrics.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

December 4—**Orthopaedics for Attorneys.** Seattle. Saturday. Sheraton Hotel: Contact: U/W.

December 6-7—**American College of Physicians MKSAP IV.** Seattle. Monday-Tuesday. U/W Health Sciences Building. Contact: U/W.

December 8—**Beta-Lactam Antibiotics.** Seattle. Wednesday. Westin Hotel. Contact U/W.

December 9-10—**Aging and Elderly.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: U/W.

January 6-7—**Sex and the Family.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 21-22—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 23—**Dyslexia.** Seattle. Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 27-28—**Current Therapy in Cardiology.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

February 4-5—**Diseases of the Elderly.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 5-12—**(IDAHO) Management of Pain.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 12-19—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 14-18—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Friday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 17-18—**Soft Tissue Surgery.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

February 19-26—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Contact: U/W.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-March 5—**(IDAHO) Sports Medicine 83.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 4-5—**High-Risk Infants of the 1980s.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

March 5-12—**(HAWAII) Future Directions and Update on Family Practice.** Kona. Saturday-Saturday. Sheraton Royal Waikiloa. Contact: U/W.

March 5-12—**(IDAHO) Management of Obesity.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 11-12—**Nutrition and Bone Metabolism.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

March 11-12—**Sex Offenders. Seattle.** Thursday-Friday. U/W South Campus Center. Contact: U/W.

March 16-18—**MKSAP: Medical Knowledge Self-Assessment Program.** Seattle. Wednesday-Friday Virginia Mason Medical Center. Contact: VMMC.

March 18—**Endocrine Day.** Seattle. Friday. U/W CDMRC. Contact: U/W.

March 18-19—**Recent Developments in Occupational Medicine.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

March 19-26—**(HAWAII) Advances in Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 25-26—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 26-April 2—**(HAWAII) Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Pathology Day.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

April 1-2—**Compensation Law/Public Policy/Back Pain.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 11-22—**Rehabilitation Medicine Review.** Seattle. Sunday-Thursday. Sheraton. Contact: U/W.

April 28-29—**Financial Planning for Physicians.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

May 6—**Primary Care Urology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13—**Medical Alumni Day.** Seattle. Thursday. U/W Health Sciences Building. Contact: U/W.

May 13-14—**Hypertension.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 20-21—**Prescription and Nonprescription Drugs.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 26-27—**Clinical Neurogenetics.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

June 3—**Endocrine Day.** Seattle. Friday. CDMRC. Contact: U/W.

June 3-4—**Acute Medical Problems.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

June 9-11—**Common Office Procedures.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

June 22-24—**Burn.** Seattle. Tuesday-Thursday. Sheraton Hotel. Contact: U/W.

(Continued on Page 60)

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U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: May 28-31, 1983, Cordova.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: May 19-21, 1983, Doubletree Inn, Tucson.

California Medical Association—731 Market St., San Francisco 94103. (415) 777-2000. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. (303) 861-1221. Annual Meeting: 1983—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-14, 1982, Hilton Hawaiian Village, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 20-23, 1983, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1983—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 12-15, 1983, Elko Convention Center, Elko.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 247-0539. Annual Meeting: May 4-6, 1983. Four Seasons Motor Hotel, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: November 3-5, 1982, Thunderbird, Jantzen Beach.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1983—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: October 7-10, 1982, Towne Motel, Yakima.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Winter Seminar: January 21-22, 1983, Rawlins; Annual Meeting: June 29-July 2, 1983, Jackson Lake Lodge, Moran.

(Continued from Page 58)

June 23-24—**Nosocomial Infections Herpes Hepatitis.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

June 27-29—**(OREGON) Office Management of Common Psychiatry Problems.** Sun River. Sunday-Tuesday. Sun River Hotel. Contact: U/W.

July 21-22—**American College of Physicians MKSAP VI.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

July 28—**Wound Healing.** Seattle. Wednesday. Westin Hotel. Contact: U/W.

July 28-30—**Debates in Otolaryngology.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

July 29-30—**Trauma and Burns.** Seattle. Wednesday-Thursday. Westin Hotel. Contact: U/W.

July 29-31—**Washington State Society of Anesthesiologists: Seafair V Anesthesia Meeting.** Seattle. Sheraton. Contact: Washington State Society of Anesthesiology, Marcia Wahlman, Executive Secretary, 2033 Sixth Avenue, Suite 900, Seattle, WA 98212. (206) 623-4801.

August 4-5—**Sports Medicine Summer 1983.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

August 18-19—**Advances in Behavioral Medicine.** Seattle. Wednesday-Friday. U/W South Campus Center. Contact: U/W.

August 25-26—**Urology for Urologists.** Seattle. Wednesday-Thursday. U/W South Campus Center. Contact: U/W.

WYOMING

January 21-22—**Wyoming Medical Society Winter Seminar.** Rawlins. Friday-Saturday. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

June 29-July 2—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

Index to
The Western Journal of Medicine Advertising

AMERICAN MEDICAL ASSOCIATION 54
AYERST LABORATORIES
Inderide 8, 9, 10
Prem Tabs/Vag Cream 41, 42, 43, 44
BANK OF AMERICA 3
BANKERS INVESTMENT CO., THE 33
BLUE SHIELD OF CALIFORNIA 27
BOOTS PHARMACEUTICAL CO.
Rufen 39, 40
Ru-Tuss 19, 20, 21, 22
CALIFORNIA MEDICAL ASSOCIATION
112th Annual Session 30, 31
CLASSIFIED 36, 48
COOPERATIVE OF AMERICAN PHYSICIANS
Mutual Protection Trust 59
CPS MEDICAL BILLING SYSTEMS 32
CUTTER LABORATORIES INC. 49
DOCTORS' CO., THE 24
ELI LILLY & CO.
Keflex 47
FAMILY HEALTH PROGRAM 49
INSURANCE CORPORATION OF AMERICA 28, 29
INTERNATIONAL MEDICAL EDUCATION CORPORATION
Postgraduate Seminars 14
KEY PHARMACEUTICALS INC.
Theo-Dur 12, 13, 14
LEDERLE LABORATORIES
TB TINE 51, 52
MARCUS ELECTRONIC DEVELOPMENT INC. 35
NORCAL MUTUAL INSURANCE CORPORATION 6
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 16
PRACTICE SERVICE CORPORATION 37
PROFESSIONAL MEDICAL SOFTWARE 25
RESEARCH INDUSTRIES INC.
Rimso-50, Rimso-100 23
ROCHE LABORATORIES
Dalmane ..... 3rd and 4th covers
Valium ..... 2nd cover, 1, 2
Medical Education 17, 18
SMITH KLINE & FRENCH LABORATORIES
Dyazide 38
STAFF RESOURCES INC. 33
UNIVERSITY OF HAWAII
Sports Medicine Course 2
UNIVERSITY OF SOUTHERN CALIFORNIA AND THE LOS ANGELES UROLOGICAL SOCIETY
Urological Cancer Symposium 52
UNIVERSITY OF UTAH SCHOOL OF MEDICINE
Snowbird Conference 52
UPJOHN CO., THE
Motrin 5
WESTERN JOURNAL OF MEDICINE, THE
Subscription 57
WISELY FOODS
Saffola Margarine 55

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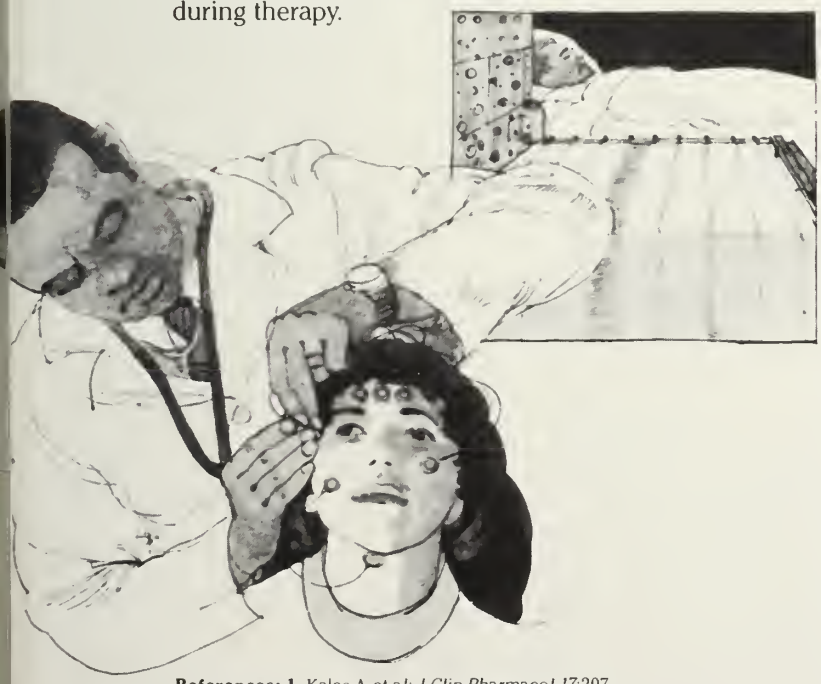

References: 1. Kales A *et al: J Clin Pharmacol 17*:207-213, Apr 1977 and data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Kales A: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **3.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **4.** Kales A *et al: JAMA 241*:1692-1695, Apr 20, 1979. **5.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 15, 1978. **6.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **7.** Kales A, Kales JD: *Pharmacol Physicians 4*:1-6, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **9.** Dement WC *et al: Behav Med 5*:25-31, Oct 1978. **10.** Vogel GW: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **11.** Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington, DC, May 3-7, 1971. **12.** Pollak CP, McGregor PA, Weitzman ED: The effects of flurazepam on daytime sleep after acute sleep-wake cycle reversal. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh, Scotland, June 30-July 4, 1975. **13.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

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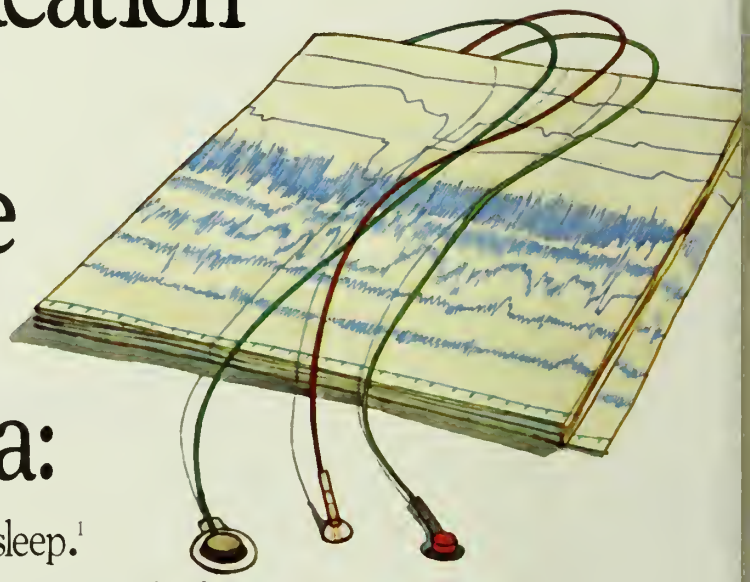

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- Seldom produces morning hangover.[3]
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PECIAL ISSUE ON OCCUPATIONAL MEDICINE ■ TABLE OF CONTENTS ON FIFTH PAGE

In the treatment of insomnia

Good mornings start with restful nights.

Dalmane *(flurazepam HCl/Roche)* patients fall asleep faster, sleep longer and seldom awaken with morning hangover.

Feeling well rested in the morning usually means having slept well the night before. And for insomniac patients receiving hypnotic therapy, a good morning also means awakening with few side effects from their medication. Many physicians choose Dalmane for their patients who suffer from insomnia for this very reason.

Aside from enabling patients to fall asleep more quickly and sleep longer, Dalmane seldom causes morning hangover. Most Dalmane patients feel alert and refreshed when they awaken. In 53 paired-night clinical studies comparing Dalmane and placebo in 2010 insomniac patients with a variety of secondary diagnoses, most Dalmane patients awakened more alert and refreshed, and less groggy and drowsy, than on nights when they had taken only placebo.[1] In a double-blind crossover study of 42 patients in private practice, approximately three times as many patients reported feeling refreshed and alert upo awakening after a night on Dalmane (flurazepam/Roche compared to placebo nights.[2] This difference was highly significant ($p<0.001$). And a retrospective study of 25 hospitalized patients who received Dalmane revealed onl a 3.1% incidence of side effects.[3]

While residual effects from Dalmane therapy are infrequent, patients should be cautioned about drinking alcohol, driving or operating hazardous machinery after ingesting the drug.

Efficacy and safety in a broad range of patient types.

Over 2000 clinical trials involving more than 10,000 patients have shown that Dalmane patients fall asleep sooner, sleep longer and experience fewer nocturn awakenings.[4] The safety and efficacy of Dalmane have been demonstrated in medical and surgical hospitalized patients, in patients seen in office practice and in elderly patients.[5-8] Since the risk of oversedation, dizziness, confu

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sion and/or ataxia increases with larger doses in the elderly, it is recommended that the dosage be limited to 15 mg.

Moreover, the efficacy and safety of Dalmane for the treatment of insomnia have been demonstrated in thousands of patients with a variety of primary medical conditions, including cardiovascular, neuropsychiatric, endocrine-metabolic, gastrointestinal, genitourinary, respiratory and musculoskeletal disorders.[1] Dalmane (flurazepam HCl/Roche) is contraindicated in pregnancy and in patients hypersensitive to the drug.

Avoids rebound insomnia upon discontinuation.

Rebound insomnia—a worsening of sleep beyond pretherapy levels after drug discontinuation—has been reported as a potential clinical problem with some hypnotics.[9,10] However, this problem has not been reported with Dalmane. In eight out of eight sleep laboratory studies, there were no reports of rebound insomnia.[11] When you prescribe Dalmane, you can be confident of efficacy that enhances therapeutic progress. Your insomniac patients can be assured of a restful night, night after night—a good start for a good morning.

References: **1.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **3.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **4.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **5.** Meyer JA, Kurland KZ: *Milit Med 138*:471-474, Aug 1973. **6.** Feffer HL, Gibbons B: *Med Times 101*(8):130-135, Aug 1973. **7.** Jacobson A *et al*: *Psychophysiology 7*:345, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **9.** Kales A, Scharf MB, Kales JD: *Science 201*:1039-1041, Sep 1978. **10.** Kales A *et al*: *JAMA 241*:1692-1695, Apr 1979. **11.** Monti JM: *Methods Find Exp Clin Pharmacol 3*(5):303-326, 1981.

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

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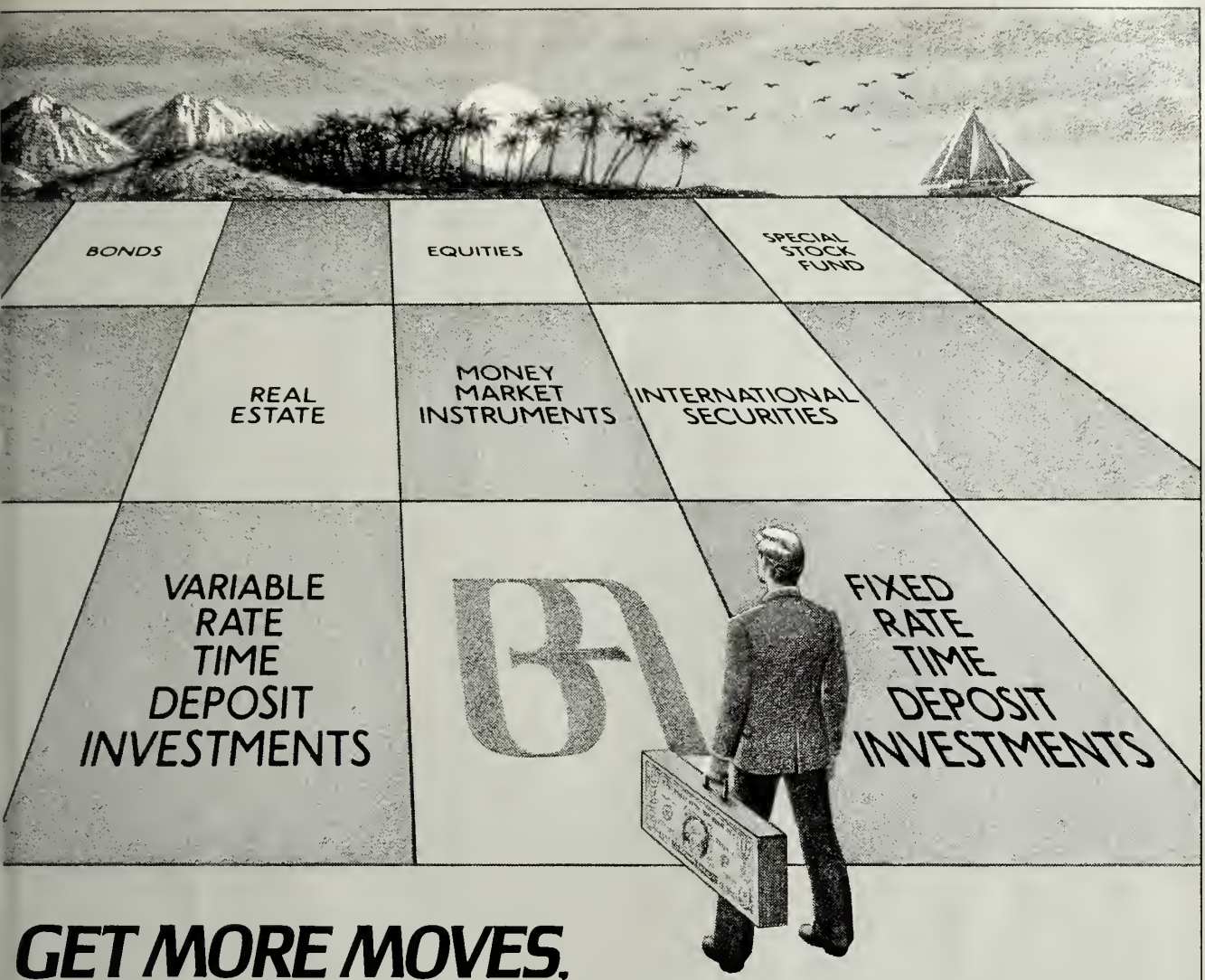

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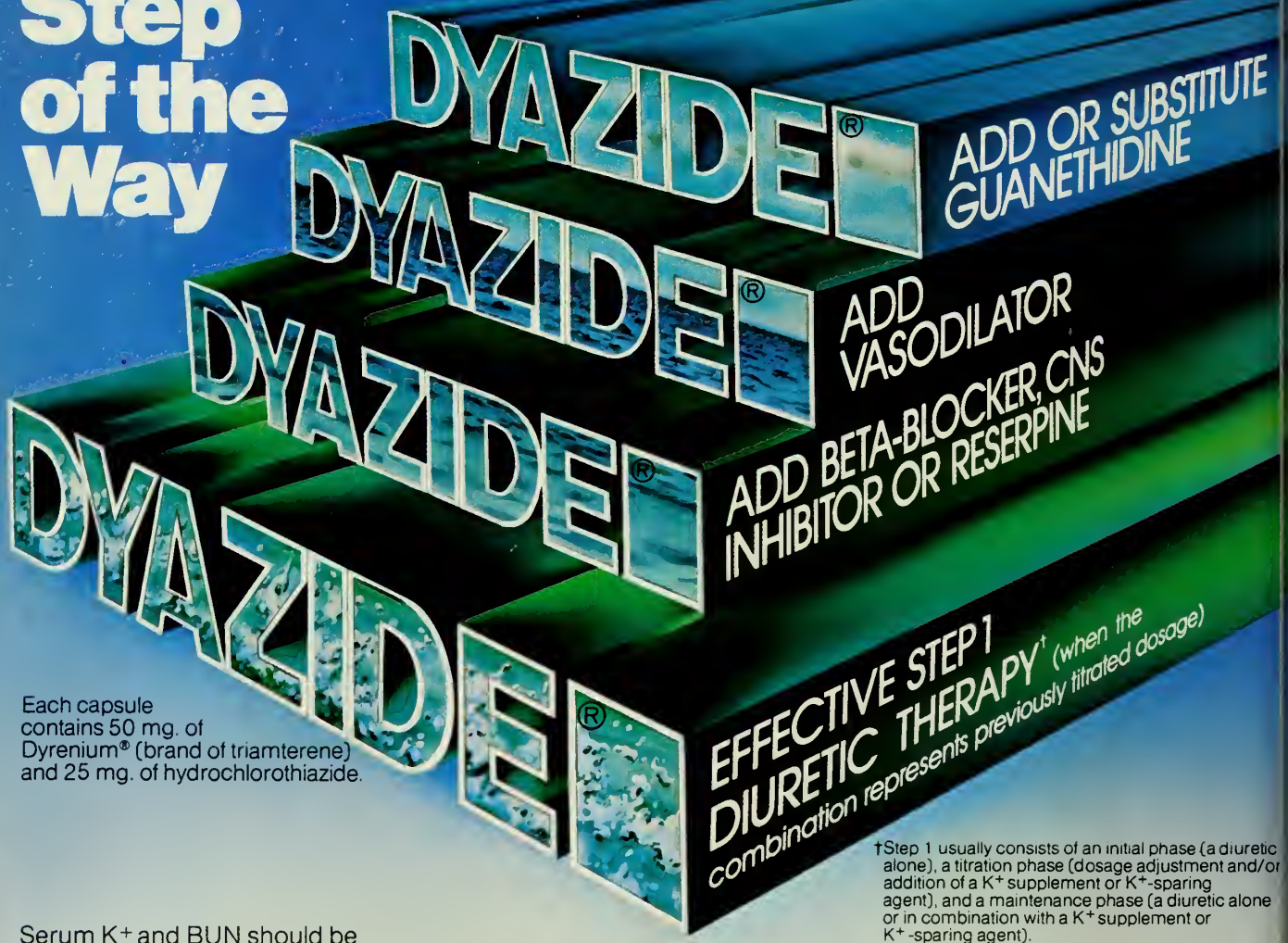

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent), and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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VOLUME 137 • NUMBER 6 • DECEMBER 1982

TABLE OF CONTENTS

OCCUPATIONAL DISEASE—NEW VISTAS FOR MEDICINE

477 *Introduction: The Tip of a Huge Iceberg?* MALCOLM S. M. WATTS, MD

478 *Occupational Medicine—Long History and Bright Future* CHARLES E. BECKER, MD
Dr. Becker is Associate Professor of Medicine, School of Medicine, University of California, San Francisco; and Chief, Division of Occupational Medicine and Toxicology, and Associate Director, Northern California Occupational Health Center, San Francisco General Hospital Medical Center, San Francisco.

480 *Occupational Asthma* DEAN SHEPPARD, MD
From the Medical Service and the Northern California Occupational Health Center, San Francisco General Hospital Medical Center, and the Cardiovascular Research Institute and the Department of Medicine, School of Medicine, University of California, San Francisco.

486 *Perspectives in Occupational Dermatology* C. G. TOBY MATHIAS, MD, and HOWARD I. MAIBACH, MD
From the Medical Service and the Northern California Occupational Health Center, San Francisco General Hospital Medical Center, and the Departments of Medicine and Dermatology, School of Medicine, University of California, San Francisco.

493 *Occupational Peripheral Neuropathies*
MARCELLO LOTTI, MD; CHARLES E. BECKER, MD, and MICHAEL J. AMINOFF, MD
From the Medical Service and the Northern California Occupational Health Center, San Francisco General Hospital Medical Center, and the Departments of Medicine and Neurology, School of Medicine, University of California, San Francisco.

499 *Hearing Conservation in Industry* ROBERT A. DOBIE, MD
Dr. Dobie is Associate Professor, Department of Otolaryngology, University of Washington School of Medicine, and Chief, Otolaryngology, Veterans Administration Medical Center, Seattle.

506 *Effects on the Liver of Chemicals Encountered in the Workplace* SUSAN M. POND, MBBS, MD
From the Medical Service and the Northern California Occupational Health Center, San Francisco General Hospital Medical Center, and the Department of Medicine, School of Medicine, University of California, San Francisco.

515 *Occupational Work Evaluation of Patients With Cardiac Disease: A Guide for Physicians*
ROBERT FRANK DeBUSK, MD, and CHARLES ANDREW DENNIS, MD
From the Division of Cardiology, Department of Medicine, Stanford University School of Medicine, Stanford, California.

521 *Male Occupational Reproductive Hazards* M. DONALD WHORTON, MD
From the Environmental Health Associates, Inc., Berkeley, California.

525 *Health Effects of Shift Work* JOSEPH LaDOU, MD
Dr. LaDou is Associate Clinical Professor of Medicine, School of Medicine, University of California, San Francisco, and Medical Director, Peninsula Industrial Medical Clinic, Sunnyvale, California.

531 *Occupational and Community Exposures to Toxic Metals: Lead, Cadmium, Mercury and Arsenic*
PHILIP J. LANDRIGAN, MD, MSc
From the Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease Control, Cincinnati.

(Continued on Page 7)

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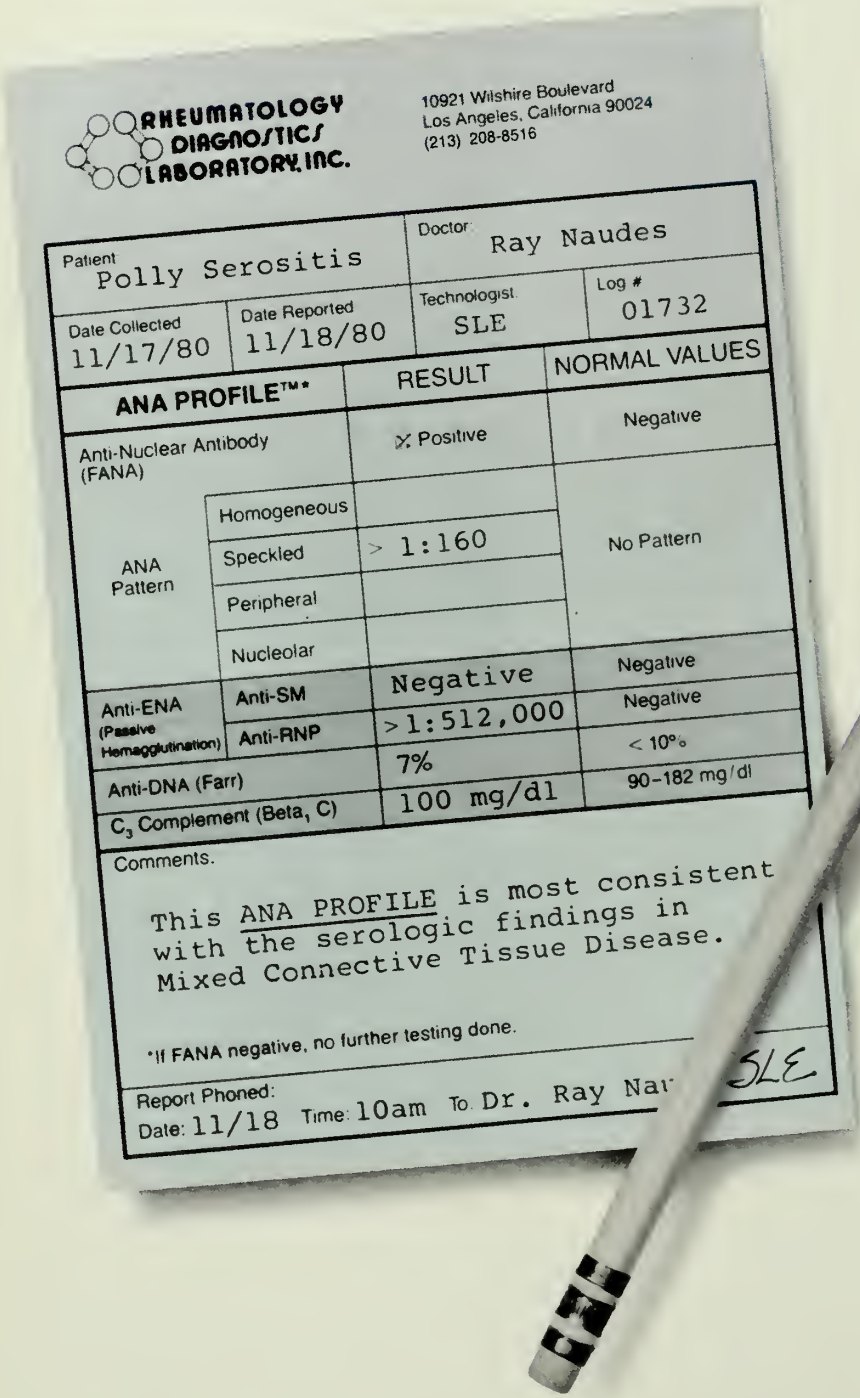

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(Continued from Page 5)

540 *Ionizing Radiation and Its Risks* MARVIN GOLDMAN, PhD
From the Laboratory for Energy-Related Health Research, University of California, Davis, Davis, California.

548 *Diffuse Malignant Mesothelioma: A Review* WILLIAM N. ROM, MD, and JAMES E. LOCKEY, MD
From the Rocky Mountain Center for Occupational and Environmental Health, Division of Respiratory, Critical Care, and Occupational (Pulmonary) Medicine, Departments of Internal Medicine and Family and Community Medicine, University of Utah School of Medicine, Salt Lake City.

555 *Occupational Epidemiology: Detection of Cancer in the Workplace*
JOHN M. PETERS, MD; WILLIAM E. WRIGHT, MD, and DAVID H. GARABRANT, MD
From the Division of Occupational Health, Department of Family and Preventive Medicine, University of Southern California School of Medicine, Los Angeles.

560 *The Hazard Evaluation System and Information Service: A Physician's Resource in Toxicology and Occupational Medicine*
KIM HOOPER, PhD
Dr. Hooper is Chief, Hazard Evaluation System and Information Service, State of California Department of Health Services and Department of Industrial Relations, Berkeley, California.

572 *Industrial Hygiene Data: Compliance, Dosage and Clinical Relevance*
STEPHEN M. RAPPAPORT, PhD; ROBERT C. SPEAR, PhD, and JANICE W. YAGER, PhD
From the Northern California Occupational Health Center, School of Public Health, University of California, Berkeley, California.

577 *The Evolution of Occupational Health and the Role of Government* RICHARD WADE, PhD, MPH
Dr. Wade is Deputy Chief for Health, Division of Occupational Safety and Health, State of California Department of Industrial Relations, San Francisco.

581 *Key Elements of the Occupational History for the General Physician* CHARLES E. BECKER, MD
Dr. Becker is Associate Professor of Medicine, School of Medicine, University of California, San Francisco; and Chief, Division of Occupational Medicine and Toxicology, and Associate Director, Northern California Occupational Health Center, San Francisco General Hospital Medical Center, San Francisco.

BOOK REVIEWS

524 *Recent Advances in Occupational Health*
Edited by J. C. McDONALD, MD, FRCP, FFCM, FFOM
Reviewed by LINDA HAWES CLEVER, MD

583 *Cancer Mortality and Morbidity Statistics: Japan and the World*
Edited by MITSUO SEGI, SUKETAMI TOMINAGA, KUNIO AOKI and ISABURO FUJIMOTO
Reviewed by CALVIN ZIPPIN, ScD

OTHER FEATURES

584 *Consultants for 1982*
The editors acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given to the journal during the past year.

585 *Volume Index*

New Training Opportunities in Occupational Health, See Page 498

Medical Practice Questions, See Pages 530, 554, 559 and 576

Subscription Information, See Advertising Page 9

Continuing Medical Education Activities in California, Hawaii and Nevada; Alaska; Idaho; Montana; New Mexico; Oregon; Utah; Washington; Wyoming, See Advertising Page 11

Information for Authors, See Advertising Page 44

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February 4-6—**21st Clinical Conference in Pediatric Anesthesiology.** Childrens Hospital at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $175. Contact: Wayne Herbert, MD, Childrens Hosp., 4650 Sunset Blvd., Los Angeles 90027. (213) 669-2262.

February 13-18—**11th Obstetric Anesthesia Conference.** Ohio State University at Maui Surf Hotel, Maui, and Sheraton Waikiki, Oahu. Sunday-Friday. 25 hrs. Contact: Ohio State Univ. Hospitals, Dept. of Anesthesiology, 410 W. 10th Ave., Columbus, OH 43210. (614) 421-8487.

CANCER

January 14-15—**Urological Cancer Symposium.** USC and Los Angeles Urological Society at USC. Friday-Saturday. 21 hrs. Contact: Trudy Mackel, 1940 Turrell St., Lomita 90717. (213) 326-7418.

February 4-6—**Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 15-18—**Clinical Hematology and Oncology.** See Medicine, February 15-18.

March 5-6—**Hyperthermia and Radiation Therapy in the Treatment of Cancer—18th Annual Cancer Symposium.** West Coast Cancer Foundation at Sheraton Palace, San Francisco. Saturday-Sunday. 12 hrs. $115 before Feb. 1; $140, thereafter. Contact: WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

March 9-11—**Current Approaches to Radiation Oncology, Biology and Physics.** UCSF at Fairmont, San Francisco. Wednesday-Friday.

April 9—**Oncology Update Symposium.** Northridge Hospital Medical Center at Biltmore Hotel, Los Angeles. Saturday. 8 hrs. $125. Contact: Sandra Rozzen, Northridge Hosp. Med. Ctr., 18300 Roscoe Blvd., Northridge 91328. (213) 885-5311.

EMERGENCY MEDICINE

January 17-21—**Postgraduate Institute for Emergency Physicians—Symposium I.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 33 hrs. $425.

January 22-29—**Advanced Problems in Cardiac Emergencies.** UCSD, American Inst. of Postgraduate Education and Scripps Mem. Hosp. at Kona Surf Hotel, Kona. One week. 21 hrs. $325. Contact: AIPE, P.O. Box 2101, Del Mar 92014. (619) 454-3212.

January 28-30—**Advanced Cardiac Life Support Workshop.** Emergency Medical Associates at Ralph K. Davies Medical Center, San Francisco. Friday-Sunday. Contact: EMA, 2310 Mason St., San Francisco 94133. (415) 956-5900.

January 31-February 4—**Topics in Emergency Medicine.** UCSF at Sheraton at Fisherman's Wharf, San Francisco. Monday-Friday. 35 hrs. $350.

March 6-11—**Emergency Medicine: 1983.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 24 hrs.

March 13-18—**Fourth Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Orange Co. Emergency Dept. Nurses Assn. at Mammoth Lakes. Sunday-Friday. 23 hrs. $325. Contact: Medical Conferences, Inc., P.O. Box 52-B, Newport Beach 92662. (714) 642-7080.

March 14-18—**Postgraduate Institute for Emergency Physicians—Symposium II.** UCSD. Monday-Friday. 33 hrs. $425.

April 22-24—**Advanced Cardiac Life Support Workshops.** Emergency Medical Associates at Ralph K. Davies Medical Cen-

(Continued on Page 15)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center 2801 Atlantic Ave., Long Beach 90801. (213) 595-3837.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3708.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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1. The California Medical Association's 112th Annual Session will be held March 11-16, 1983 at _____.
2. Over 40 CME accredited courses featuring modern solutions to today's medical problems are available for physicians of all _____.
3. Professional liability, Medi-Cal and private contracting are among the many controversial issues to be discussed at CMA's policy-making _____.
4. An opportunity to view the latest in commercial and scientific technology is available in the _____.
5. A first time feature at Annual Session will be the showing of nine award winning _____.
6. Physicians and guests may save time by pre-registering before _____.

Answers: 1. the Westin Bonaventure Hotel, Los Angeles. 2. specialties. 3. House of Delegates. 4. Exposition Hall. 5. medical films. 6. February 11, 1983 (but you can register at the door).

If you didn't get the word, clip, complete and send this form to:

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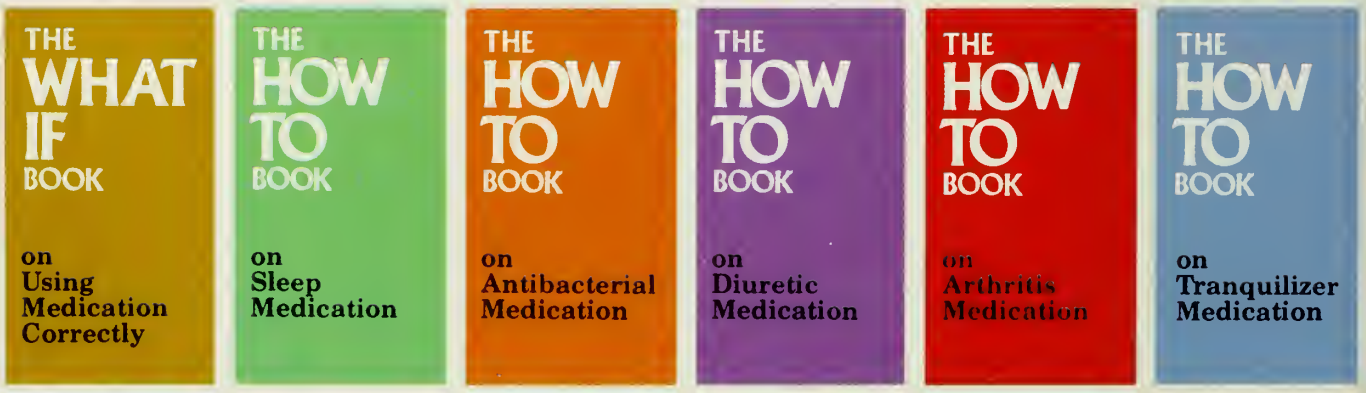

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Medicines that matter from people who care

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IF YOU ARE A PHYSICIAN, YOUR RISK* OF CONTRACTING HEPATITIS B IS...

about
1 in 500

(lift tab)

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about
1 in 5

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For many physicians the risks are unavoidable...

*based on prevalence data from a seroepidemiologic survey of medical specialties

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

MSD
MERCK SHARP & DOHME

Hepatitis B:

The consequences are unpredictable

Although hepatitis B is an unpredictable disease with a variety of presentations and outcomes, most patients recover. Persistence of viral infection (the chronic carrier state) occurs in 5 to 10 percent of persons who become infected with hepatitis B virus. Acute hepatitis B infection may be symptomatic and can incapacitate a person for weeks to months or lead to complications or chronic sequelae. However, 50 to 60 percent of all hepatitis B infections are subclinical, asymptomatic, and usually undetected. These cases have a greater risk of progression to chronic sequelae.

Sequelae of hepatitis B

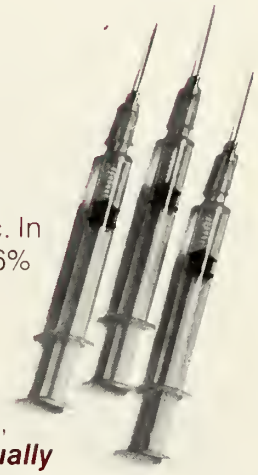
Chronic carrier state	Develops in up to 10% of patients who have had hepatitis B; occurs more frequently in anicteric cases.[2] Chronic carriers are usually asymptomatic but may develop other chronic sequelae
Chronic persistent hepatitis	Generally a benign condition; progression to cirrhosis or other late sequelae such as hepatoma is rare[3]
Chronic active hepatitis	A major late complication; occurring in approximately 3% to 5% of cases[4]
Cirrhosis	An estimated 11% of deaths due to cirrhosis are associated with hepatitis B[5]
Liver cancer	The relative risk of primary liver cancer for carriers is 273 times greater than for noncarriers[5]

For susceptible individuals at increased risk of contracting hepatitis B infection...

Merck Sharp & Dohme announces

NEW Heptavax·B®
(Hepatitis B Vaccine | MSD)

Now...the disease is preventable



Highly immunogenic

Clinical studies[6-8] have shown HEPTAVAX-B to be highly immunogenic. In one study, HEPTAVAX-B induced neutralizing antibody (anti-HBs) in 96% of vaccine recipients following the three-dose regimen.[6]

Highly effective

In clinical studies, HEPTAVAX-B was highly effective in protecting vaccine responders against acute hepatitis B, asymptomatic infection, and the chronic carrier state. In these studies,[6,7] ***the vaccine was virtually 100% effective in preventing hepatitis B in those who developed anti-HBs.***

Incidence of adverse reactions did not differ significantly from placebo

Generally well tolerated

In over 6,000 individuals administered HEPTAVAX-B during clinical trials since 1975, no serious adverse reactions attributable to vaccination were reported. In two double-blind, placebo-controlled studies[6,7] involving a total of 2,485 persons, the overall rates of adverse reactions reported by the vaccine recipients did not differ significantly from those of placebo recipients.

Injection-site soreness is the most common adverse reaction. Less common local reactions are erythema, swelling, warmth, or induration which usually subside within 48 hours.

Low-grade fever (less than 101°F) occurs occasionally and is usually confined to the 48-hour period following vaccination. Although uncommon, fever over 102°F has been reported.

Systemic complaints, including malaise, fatigue, headache, nausea, dizziness, myalgia, and arthralgia, are infrequent and have been limited to the first few days following vaccination. Rash has been reported rarely.

MSD
MERCK SHARP & DOHME

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

NEW **Heptavax·B**® Vials, 3 ml

(Hepatitis B Vaccine | MSD)

for you...
for your staff...
for your patients...

"Persons at substantial risk of HBV [hepatitis B virus] infection who are demonstrated or judged likely to be susceptible should be vaccinated."[9]

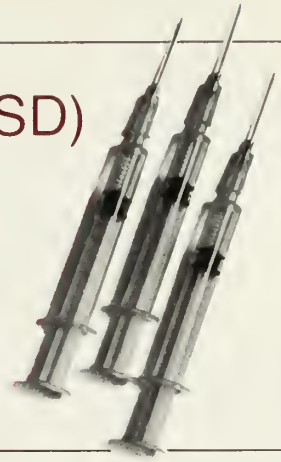
—Recommendation of the Immunization Practices Advisory Committee (ACIP)[9]

The Immunization Practices Advisory Committee (ACIP) has identified certain populations at risk of HBV infection and has recommended vaccination for appropriate members, as follows:

ACIP recommendations for vaccination against hepatitis B infection[9]	
• health-care workers • hospital staff • clients and staff of institutions for the mentally retarded • hemodialysis patients • homosexually active males • illicit injectable drug users • recipients of certain blood products • household and sexual contacts of HBV carriers	• classroom contacts of deinstitutionalized mentally retarded HBV carriers who behave aggressively • special high-risk populations from areas where hepatitis B is highly endemic Indochinese and Haitian refugees Alaskan Eskimos • inmates of long-term correctional facilities

A complete copy of the ACIP recommendations is available through your MSD Professional Representative.

Heptavax-B®(Hepatitis B Vaccine|MSD) is now available— but the current supply is limited.



For more information about the vaccine and how to obtain it, please contact your Merck Sharp & Dohme Professional Representative or call our Professional Information Service at (215) 661-7300.

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1. Denes, A. E. et al.: Hepatitis B infection in physicians: Results of a nationwide seroepidemiologic survey, JAMA *239(3)*:210-212, January 16, 1978.
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8. Krugman, S. et al.: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 μg and 40 μg doses, J. Med. Virol. *8*:119-121, 1981.
9. Inactivated hepatitis B virus vaccine, MMWR *31(24)*: 317-328, June 25, 1982.

Indications and Usage: Immunization against infection caused by all known subtypes of hepatitis B virus in persons 3 months of age or older, especially those who are at increased risk of infection with this virus; will not prevent hepatitis caused by other agents such as hepatitis A virus, non-A, non-B hepatitis viruses, or other viruses known to infect the liver.

NOTE: Further study is required to determine the effectiveness of HEPTAVAX-B in preventing hepatitis B when the vaccine regimen is begun after an exposure to the hepatitis B virus has already occurred (i.e., use for postexposure prophylaxis). However, it has been demonstrated that doses up to 3 ml of Hepatitis B Immune Globulin, when administered simultaneously with HEPTAVAX-B at separate body sites, do not interfere with the induction of neutralizing antibodies against hepatitis B virus.

Contraindications: Hypersensitivity to any component of the vaccine.

Warnings: Persons with immunodeficiency or those receiving immunosuppressive therapy may require larger vaccine doses to develop adequate circulating antibody levels.

Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time HEPTAVAX-B is given. HEPTAVAX-B may not prevent hepatitis B in such patients.

Precautions: ***General:*** As with any parenteral vaccine, epinephrine should be available for immediate use should an anaphylactoid reaction occur. Any serious active infection is reason for delaying use of this vaccine except when, in the opinion of the physician, withholding the vaccine entails a greater risk. Caution and appropriate care should be exercised in administering this vaccine to individuals with severely compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

Pregnancy: *Pregnancy Category C*—It is not known whether the vaccine can cause fetal harm when administered to pregnant women or can affect reproductive capacity; not recommended for use in pregnant women.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Caution should be exercised when this vaccine is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 3 months have not been established. Use of this vaccine in children below the age of 3 months is not recommended at present.

Adverse Reactions: HEPTAVAX-B is generally well tolerated. No serious adverse reactions attributable to vaccination have been reported during the course of clinical trials involving administration of HEPTAVAX-B to over 6,000 individuals. In two double-blind placebo-controlled studies among 2,485 persons, the overall rates of adverse reactions reported by vaccine recipients (24.3% and 21.5%) did not differ significantly from those of placebo recipients (21.4% and 18.7%). Approximately half of all reported reactions were injection-site soreness, which occurred somewhat more frequently among vaccine recipients.

Other less common local reactions have included erythema, swelling, warmth, or induration. These signs and symptoms of local inflammation are generally well tolerated and usually subside within 2 days of vaccination.

Low-grade fever (less than 101 F) occurs occasionally and is usually confined to the 48-hour period following vaccination. Although uncommon, fever over 102 F has been reported. Systemic complaints, including malaise, fatigue, headache, nausea, dizziness, myalgia, and arthralgia, are infrequent and have been limited to the first few days following vaccination. Rash has been reported rarely.

Administration: The immunization regimen consists of 3 doses of vaccine given intramuscularly. *Do not inject intravenously, subcutaneously, or intradermally.* Store at 2-8 C (35.6-46.4 F). *Do not freeze, since freezing destroys potency.* The vaccine is used as supplied. No dilution or reconstitution is necessary.

How Supplied: Vials containing 3.0 ml of liquid vaccine for use with syringes only, each ml containing 20 mcg hepatitis B surface antigen formulated in an alum adjuvant and thimerosal (mercury derivative) 1:20,000 added as a preservative.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck, Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

MSD
MERCK SHARP & DOHME

J2HV03(000)

A NEW AGE IN THE CONTROL OF ANGINA

© 1982, Pfizer Inc.

PROCARDIA®

(NIFEDIPINE) *Capsules 10 mg*

PROCARDIA is the beginning of a new age in the treatment of angina:

The Calcium Age.

It is now known that calcium ions, working at the cellular level, regulate the degree of vasoconstriction and, thereby, play a critical role in the anginal attack.

PROCARDIA acts at the cell membrane to selectively block calcium access to the contractile process in the arterial cell.

Through this action, PROCARDIA manages:
—vasospastic angina, by preventing coronary artery spasm and increasing myocardial O_2 supply
—classical effort-associated angina, by dilating peripheral arteries to reduce afterload and myocardial O_2 demand
—mixed angina, which involves elements of vasospastic and effort-associated angina

Like beta blockers, PROCARDIA reduces myocardial O_2 demand. But, unlike these agents, PROCARDIA also increases myocardial O_2 supply to both normal and poststenotic areas[1] of the myocardium by preventing coronary artery spasm.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

Please see PROCARDIA Brief Summary on last page.

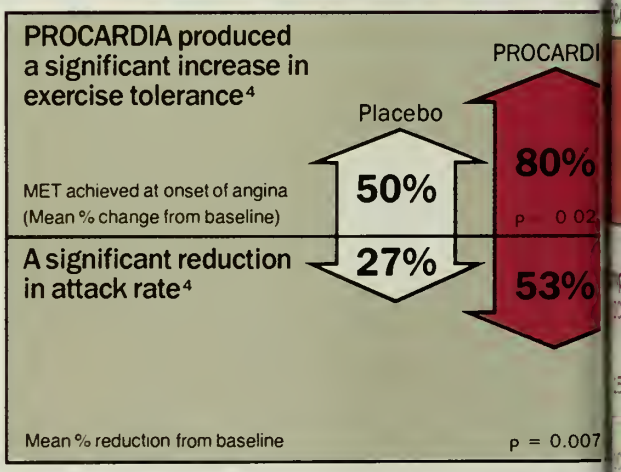
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PROVEN EFFECTIVE ACROSS THE SPECTRUM OF ANGINA

Contemporary medical opinion holds that the pathophysiology of angina is a spectrum ranging from pure, fixed atherosclerotic lesion to pure coronary artery spasm. Many patients, however, are believed to have a combination of both lesion and spasm.[2,3]

Angina due to pure fixed lesion can be prevented by reducing oxygen demand. Angina due to coronary artery spasm can be treated by preventing the spasm itself, thereby increasing oxygen supply. With this new understanding of angina, optimal antianginal therapy should provide this dual action: increasing O_2 supply while reducing O_2 demand.

In effort angina*
(when symptomatic despite conventional ther



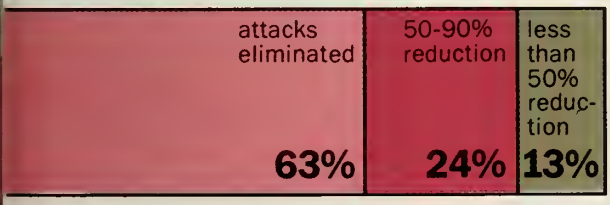
Double-blind, placebo-controlled, crossover 20-week s of 32 patients (27 evaluated for attack rate; 19 for ex tolerance). Mean PROCARDIA dosage: 51 mg/day.

*In chronic stable angina (effort-associated angina) PROCAI has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exer tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomp

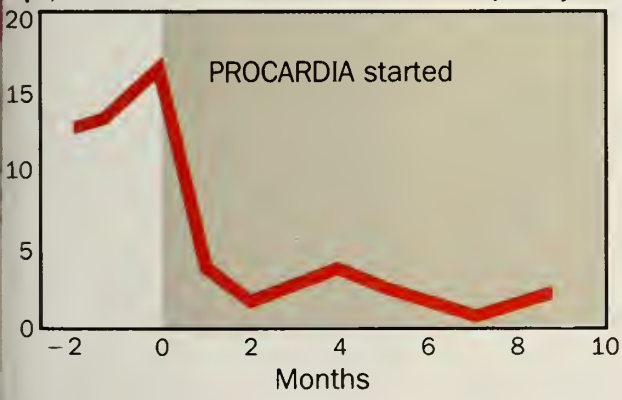
Please see PROCARDIA Brief Summary on last page.

vasospastic angina

CARDIA eliminated attacks in 63% of patients[5]

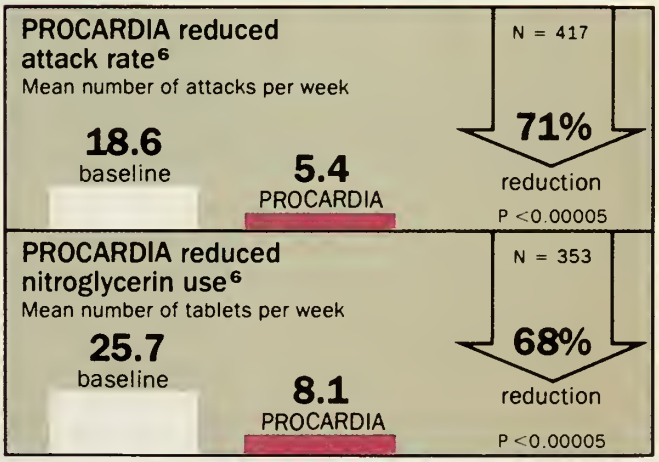


mpt, sustained decrease in attack frequency[5]



;-term, open study of 127 patients unresponsive to beta kers and/or nitrates with symptoms of myocardial emia and demonstrated coronary artery spasm. CARDIA dosage: 40 to 160 mg/day.

In mixed angina (fixed lesion and spasm)



Studies of patients with mixed angina characterized by pain at rest and effort. Most patients (89%) were initiated on nitrate and/or beta blocker therapy but remained symptomatic. Minimum duration of nifedipine treatment two months. Nifedipine dosage: 30 to 120 mg/day.

PROCARDIA®
THE FIRST ORAL CALCIUM CHANNEL BLOCKER

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

ANGINA MANAGEMENT BEYOND BETA BLOCKERS

—Beta blockers prevent angina primarily by lowering myocardial oxygen demand. Like these agents, PROCARDIA reduces myocardial oxygen demand. However, PROCARDIA provides an added dimension of angina control by increasing myocardial oxygen supply where coronary artery spasm is present.

—Beta blockers can actually cause spasm. PROCARDIA prevents spasm.

—Beta blockers decrease myocardial perfusion in poststenotic areas. PROCARDIA increases myocardial perfusion to both normal and poststenotic areas.

—Beta-blocker treatment is limited in patients with myocardial dysfunction, COPD, asthma, bundle branch blocks, and diabetes. PROCARDIA can be given safely in all these groups of patients.

—The hypotensive effect of PROCARDIA is usually modest and well tolerated, however, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or subsequent upward dosage adjustment, and may be more likely with concomitant beta blockers.

—Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA, or at the time of dosage increases. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers, if possible, rather than stopping them abruptly before beginning PROCARDIA.

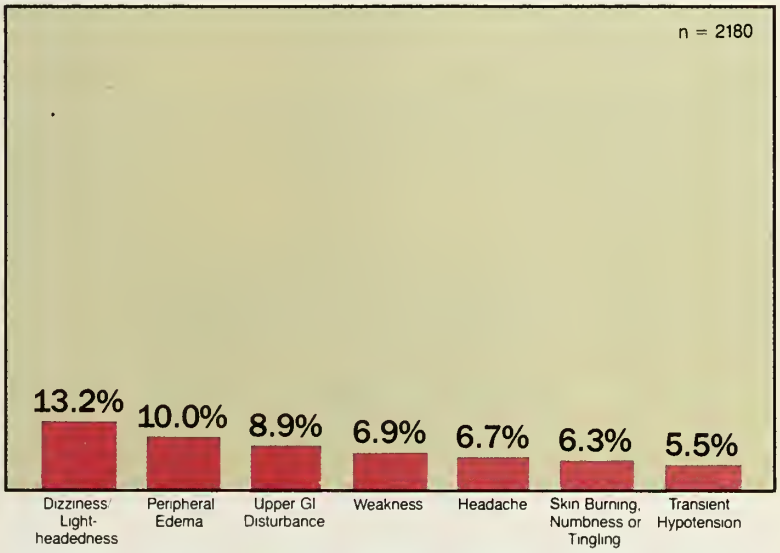
—Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

Please see PROCARDIA Brief Summary on last page.

THE FIRST ORAL CALCIUM CHANNEL BLOCKER...

PROVIDES PROTECTION WITH A MILD SIDE-EFFECT PROFILE

Most common adverse reactions



Information is drawn from a large uncontrolled experience in 2180 patients and presents the most frequent side effects reported with PROCARDIA.

AN ADDED ADVANTAGE: COMPATIBILITY

—MAY BE USED WITH A WIDE VARIETY OF OTHER AGENTS

—CAN BE USED WITH NITRATES AND BETA BLOCKERS WITH CAUTION (See Warnings and Precautions)

THE FIRST ORAL CALCIUM CHANNEL BLOCKER FOR THE MANAGEMENT OF ANGINA

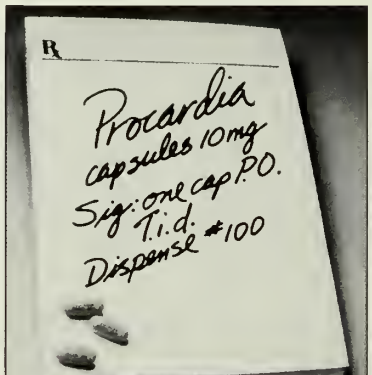
PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Proven effective when used alone.

Enhanced effectiveness when combined with beta blockers.

Convenient dosing

Start with:	1	10-mg capsule *t.i.d.*
Titrate to:	2	10-mg capsules *t.i.d.*
Titrate to:	3	10-mg capsules *t.i.d*



For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely. Maximum dose: 180 mg/day.

References

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4. Mueller HS, Chahine RA. Interim report of multicenter double-blind, placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71 645-657. October 1981.
5. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med* 302 1269–1273. June 5, 1980.
6. Braunwald E (moderator). Procardia® (nifedipine) in clinical practice. Presented at symposium following the Thirty-First Annual Scientific Session of the American College of Cardiology. Atlanta, Georgia. April 29, 1982.

PROCARDIA® CAPSULES For Ora

(nifedipine)

BRIEF SUMMARY

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifed indicated for the management of vasospastic angina confirmed by any of the f criteria: 1) classical pattern of angina at rest accompanied by ST segment el 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiogra demonstrated coronary artery spasm. In those patients who have had angic the presence of significant fixed obstructive disease is not incompatible diagnosis of vasospastic angina, provided that the above criteria are sa PROCARDIA may also be used where the clinical presentation suggests a p vasospastic component but where vasospasm has not been confirmed, e.g. pain has a variable threshold on exertion or in unstable angina where elect ographic findings are compatible with intermittent vasospasm, or when ar refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROC is indicated for the management of chronic stable angina (effort-associated without evidence of vasospasm in patients who remain symptomatic despi quate doses of beta blockers and/or organic nitrates or who cannot tolerat agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been e in controlled trials of up to eight weeks duration in reducing angina frequer increasing exercise tolerance, but confirmation of sustained effectiveness ar uation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant PROCARDIA and beta-blocking agents may be beneficial in patients with stable angina, but available information is not sufficient to predict with confide effects of concurrent treatment, especially in patients with compromised left ular function or cardiac conduction abnormalities. When introducing such conc therapy, care must be taken to monitor blood pressure closely since severe hy sion can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypo effect of PROCARDIA is modest and well tolerated, occasional patients ha excessive and poorly tolerated hypotension. These responses have usually o during initial titration or at the time of subsequent upward dosage adjustme may be more likely in patients on concomitant beta blockers.

Increased Angina/Beta Blocker Withdrawal: Occasional patients have dev well documented increased frequency, duration or severity of angina on PROCARDIA or at the time of dosage increases. The mechanism of this resp not established but could result from decreased coronary perfusion associat decreased diastolic pressure with increased heart rate, or from increased d resulting from increased heart rate alone.

Patients recently withdrawn from beta blockers may develop a withdraw drome with increased angina, probably related to increased sensitivity to ca amines. Initiation of PROCARDIA treatment will not prevent this occurren might be expected to exacerbate it by provoking reflex catecholamine release have been occasional reports of increased angina in a setting of beta blocke drawal and PROCARDIA initiation. It is important to taper beta blockers if po rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocke developed heart failure after beginning PROCARDIA. Patients with tight aor nosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases eral vascular resistance, careful monitoring of blood pressure during the initial istration and titration of PROCARDIA is suggested. Close observation is esp recommended for patients already taking medications that are known to lowe pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associate arterial vasodilation and not due to left ventricular dysfunction, occurs in about ten patients treated with PROCARDIA. This edema occurs primarily in the extremities and usually responds to diuretic therapy. With patients whose an complicated by congestive heart failure, care should be taken to differentia peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and ings.) Experience in over 1400 patients in a non-comparative clinical trial has that concomitant administration of PROCARDIA and beta-blocking agents is u well tolerated, but there have been occasional literature reports suggesting th combination may increase the likelihood of congestive heart failure, severe hy sion or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with ni but there have been no controlled studies to evaluate the antianginal effectiver this combination.

Pregnancy: Category C

ADVERSE REACTIONS: The most common adverse events include dizzin light-headedness, peripheral edema, nausea, weakness, headache and flu each occurring in about 10% of patients, transient hypotension in about 5%, p tion in about 2% and syncope in about 0.5%. Syncopal episodes did not rec reduction in the dose of PROCARDIA or concomitant antianginal medication rarely, introduction of PROCARDIA therapy was associated with an increase ginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distingui from the natural history of the disease in these patients. It remains possible, ho that some or many of these events were drug related. Myocardial infarction oc in about 4% of patients and congestive heart failure or pulmonary edema in 2%. Ventricular arrhythmias or conduction disturbances each occurred in few 0.5% of patients.

Laboratory tests: Rare, mild to moderate, transient elevations of enzymes as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, single incident of significantly elevated transaminases and alkaline phosphatas seen in a patient with a history of gall bladder disease after about eleven mon nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. Thes oratory abnormalities have rarely been associated with clinical symptoms.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA Capsule contains nifedipine. PROCARDIA Capsules are supplied in amber glass bottles c capsules (NDC 0069-2600-66).

The capsules should be protected from light and moisture and stored at cont room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original conta

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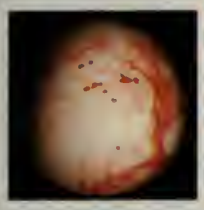
Pfizer LABORATORIES DIVISION
PFIZER INC.

WE HAVE A SOLUTION FOR A DIFFICULT UROLOGICAL PROBLEM

The Problem

SYMPTOMS:

EARLY
INTERSTITIAL CYSTITIS



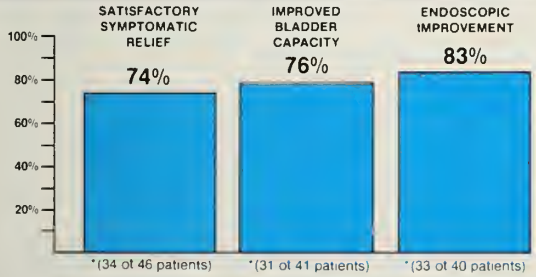
CLASSICAL
INTERSTITIAL CYSTITIS

- irritative voiding symptoms
- suprapubic pain
- functional bladder capacity reduced
- anatomical bladder capacity:
  EARLY — normal
  CLASSICAL — reduced
- vesical mucosa:
  EARLY — normal appearing
  CLASSICAL — ulcerated, scarred
- submucosal vesical hemorrhages observed following second overdistension

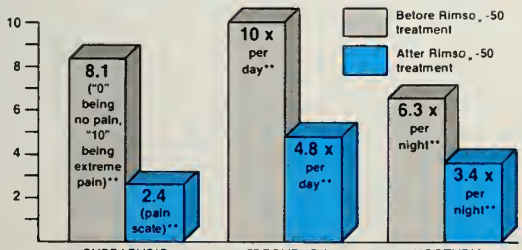
DIAGNOSIS: INTERSTITIAL CYSTITIS

The Solution

Rimso®-50
brand of
STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE



* STEWART, B.H., et al., J. Urol., 36:116, 1976



** Data on File — Research Industries Corporation

FOR FURTHER INFORMATION WJ12/82

RESEARCH INDUSTRIES CORPORATION
1847 West 2300 South
Salt Lake City, Utah 84119
Toll-Free 1-800-453-8432

Name

Address

City State Zip

Rimso®-50
(dimethyl sulfoxide)
50% w/w aqueous solution

INDICATIONS AND USAGE: Rimso®-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. Rimso®-50 has not been approved as being safe and effective for any other indication. There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.
CONTRAINDICATIONS: None known.
WARNINGS: Dimethyl sulfoxide can initiate the liberation of histamine and there has been occasional hypersensitivity reaction with topical administration of dimethyl sulfoxide. This hypersensitivity has been reported in one patient receiving intravesical Rimso®-50. The physician should be cognizant of this possibility in prescribing Rimso®-50. If anaphylactoid symptoms develop, appropriate therapy should be instituted.
PRECAUTIONS: Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rabbits given high doses of dimethyl sulfoxide chronically. Since lens changes were noted in animals, full eye evaluations, including slit lamp examinations, are recommended prior to and periodically during treatment. Approximately every six months patients receiving dimethyl sulfoxide should have a biochemical screening, particularly liver and renal function tests, and complete blood count.

Intravesical instillation of Rimso®-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation. Some data indicate that dimethyl sulfoxide potentiates other concomitantly administered medications.

Pregnancy Category C. Dimethyl sulfoxide caused teratogenic responses in hamsters, rats, and mice when administered intraperitoneally at high doses (2.5-12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days 3 through 16 of gestation failed to produce any abnormalities. There are no adequate and well controlled studies in pregnant women. Dimethyl sulfoxide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dimethyl sulfoxide is administered to a nursing woman.

Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: A garlic-like taste may be noted by the patient within a few minutes after instillation of Rimso®-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours.

Transient chemical cystitis has been noted following instillation of dimethyl sulfoxide. The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.
DOSAGE AND ADMINISTRATION: Instillation of 50 ml of Rimso®-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately.

Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of Rimso®-50 can reduce bladder spasm.

In patients with severe interstitial cystitis with very sensitive bladders, the initial treatment, and possibly the second and third (depending on patient response) should be done under anesthesia (Saddle block has been suggested).
HOW SUPPLIED:
Bottles contain 50 ml of sterile and pyrogen-free Rimso®-50 (50% w/w dimethyl sulfoxide aqueous solution).
Dimethyl sulfoxide is clear and colorless.
Protect from strong light.
Store at room temperature (15° to 30° C).
Do not autoclave.
NDC #0433-0433-05.

*Stewart, B.H., et al., J. Urol., 36:116, 1976

NEW PRODUCT

Rimso®-100
brand of
STERILE AND PYROGEN-FREE DIMETHYL SULFOXIDE

CRYOPRESERVATIVE SOLUTION
(99.0 + concentration)

Available in:

10 ml ampules, 10 ampules/case
70 ml bottles, 6 bottles/case
70 ml multi-dose containers, 6 bottles/case

BECAUSE
A THIAZIDE ALONE
CAN ONLY DO
SO MUCH...
AND YET
CAN DO
TOO MUCH.
E. M. I.

INCREASE CONTROL WITHOUT INCREASING POTASSIUM PROBLEMS.

A dependable means to long-term blood pressure control.

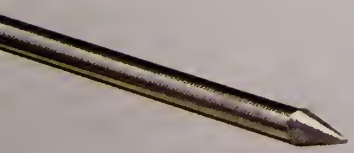
Many times, a diuretic alone can't keep hypertension in check. INDERIDE, however, can pick up where thiazide therapy leaves off.

The combination of propranolol HCl, the world's most trusted beta blocker, and hydrochlorothiazide, the standard among diuretics, enables INDERIDE to exert an additive antihypertensive effect.[1,2] In fact, a propranolol/hydrochlorothiazide regimen maintained blood pressure below 90 mm Hg in 81.8% to 86.4% of patients followed for 6 to 18 months of therapy.[1]

Low thiazide dosage means reduced risk of hypokalemia.

When thiazides are prescribed in doses greater than 50 mg/day, the potential for hypokalemia increases substantially. What's more, the greater the fall in serum K^+, the greater the risk of hypokalemia-induced PVCs.[3,4]

With INDERIDE, the additive hypotensive effect of propranolol HCl allows the effective dose of hydrochlorothiazide to be kept low (25 mg b.i.d.). And by lowering the daily dose of diuretic, INDERIDE also lowers the potential for diuretic-induced side effects. Potassium problems are less likely to occur—yet blood pressure can be controlled consistently.



INDERIDE®

Each tablet contains INDERAL® (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

When you know you need more than a thiazide.

Please see Brief Summary of Prescribing Information on following page.

INDERIDE®

Each tablet contains INDERAL (propranolol HCl) 40 mg or 80 mg, and hydrochlorothiazide 25 mg

B.I.D. 40/25 80/25

NEW TABLET SHAPE ™

The appearance of these tablets is a trademark of Ayerst Laboratories

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

INDERIDE®
BRAND OF
propranolol hydrochloride (INDERAL®)
and hydrochlorothiazide

No. 484 – Each INDERIDE®-40/25 tablet contains		
	Propranolol hydrochloride (INDERAL®)	40 mg
	Hydrochlorothiazide	25 mg
No. 488 – Each INDERIDE®-80/25 tablet contains		
	Propranolol hydrochloride (INDERAL®)	80 mg
	Hydrochlorothiazide	25 mg

WARNING: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

INDICATION: INDERIDE is indicated in the management of hypertension. (See boxed warning.)

CONTRAINDICATIONS: Propranolol hydrochloride (INDERAL®): Propranolol hydrochloride is contraindicated in: 1) bronchial asthma, 2) allergic rhinitis during the pollen season, 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock, 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol, 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

Hydrochlorothiazide: Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS: Propranolol hydrochloride (INDERAL®): CARDIAC FAILURE. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be immediately withdrawn, b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction following *abrupt* discontinuation of propranolol therapy. Therefore, when discontinuance of propranolol is planned the dosage should be gradually reduced and the patient carefully monitored. In addition when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long-term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS UNDERGOING MAJOR SURGERY beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, propranolol should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since propranolol is a competitive inhibitor of beta-receptor agonists its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA) propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA. Because of its beta-adrenergic blocking activity, propranolol may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. In patients with impaired renal function, cumulative effects of the drug may develop.

Thiazides should also be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

USE IN PREGNANCY: Propranolol hydrochloride (INDERAL®): The safe use of propranolol in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers. Thiazides appear in breast milk. If the use of the drug is deemed essential, the patient should stop nursing.

PRECAUTIONS: Propranolol hydrochloride (INDERAL®): Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if propranolol is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of propranolol may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause are: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or during concomitant use of corticosteroids or ACTH.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (*e.g.*, increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements such as foods with a high potassium content.

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

ADVERSE REACTIONS: Propranolol hydrochloride (INDERAL®): *Cardiovascular:* bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands, arterial insufficiency, usually of the Raynaud type, thrombocytopenic purpura.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Hydrochlorothiazide: *Gastrointestinal:* anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia.

Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

HOW SUPPLIED: – Each hexagonal-shaped, off-white, scored INDERIDE 40/25 tablet is embossed with an "I" and imprinted with "INDERIDE 40/25," contains 40 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0484-81) and 1,000 (NDC 0046-0484-91). Also in unit dose package of 100 (NDC 0046-0484-99).

– Each hexagonal-shaped, off-white, scored INDERIDE 80/25 tablet is embossed with an "I" and imprinted with "INDERIDE 80/25," contains 80 mg propranolol hydrochloride (INDERAL®) and 25 mg hydrochlorothiazide, in bottles of 100 (NDC 0046-0488-81) and 1,000 (NDC 0046-0488-91). Also in unit dose package of 100 (NDC 0046-0488-99).

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Store at room temperature (approximately 25° C).

7996/882

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

(Continued from Page 15)

pril 11-14—**Renal, Acid-Base and Electrolyte Disorders for the Practicing Physician.** LLU at Mauna Kea Beach Hotel, Kamuela. Monday-Thursday. 16 hrs.

pril 24-29—**American Academy of Neurology.** Town and Country, San Diego. Sunday-Friday. Contact: AAN, 2221 University Ave., S.E., Minneapolis 55414.

BSTETRICS AND GYNECOLOGY

anuary 29—**Ovulation Update: 1983.** Scripps Clinic and Research Foundation, La Jolla. Saturday. 6 hrs. $75. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 455-9100.

ebruary 5-11—**Perinatal Medicine.** USC at Royal Lahaina, Maui. One week. 23 hrs. $425.

ebruary 6-11—**OB/GYN Update.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 22 hrs.

ebruary 12-13—**OB-GYN Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton, Beverly Hills. Saturday-Sunday. 10 hrs. $80. Contact: Dir. of Med. Ed., L.A. OB-GYN Soc., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

ebruary 14-18—**38th Annual Postgraduate Assembly.** OB-GYN Assembly of So. Calif. at Beverly Hilton, Beverly Hills. Monday-Friday. 28 hrs. $375. Contact: Dir. of Med. Ed., OB-GYN Assembly of So. Calif., 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

larch 12-19—**Office Gynecology.** Univ. of Washington School of Medicine at Sheraton Waikoloa, Kona. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

larch 20-23—**OB/GYN for the Practicing Physician.** UCSF at Yosemite. Sunday-Wednesday.

EDIATRICS

anuary 12—**22nd Annual Parmelee Memorial Lecture.** Los Angeles Pediatric Society at Hilton, Los Angeles. Wednesday. 4½ hrs. Contact: Eve Black, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

anuary 31-February 3—**8th Annual Winter Ski and Study Symposium.** Calif. Chapters 1 and 2, American Academy of Pediatrics, at Caesar's, Lake Tahoe. Monday-Thursday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

ebruary 17-19—**Pediatric Urology.** See Surgery, February 17-19.

ebruary 23-March 1—**Adolescent/Young Adult Medicine.** Hurley Medical Center at Wailea Beach Hotel, Maui. One week. 20 hrs. Contact: Hurley Med Ctr., Dept. of Cont. Med. Ed., One Hurley Plaza, Flint, MI 48504. (313) 766-0142.

larch 3-5—**Advances in Pediatric Infectious Diseases.** Children's Hospital Medical Center of Northern Calif. at Sahara Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes-Dodd, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609. (415) 428-3334.

larch 10-13—**Combined Southern California Pediatric Postgraduate Meeting.** Calif. Chap. 2, American Academy of Pediatrics, at Hilton Riviera, Palm Springs. Thursday-Sunday. Contact: Eve Black, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

larch 19-26—**Updates in Pediatrics: An Epic Medical Expedition.** American Institute of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

pril 8-9—**Pediatric Topics.** UCD at Sacramento Inn, Sacramento. Friday-Saturday. 10 hrs.

(Continued on Page 37)

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Cancer of the Prostate — Chronic Lymphocytic Leukemia — Hodgkins Disease — Cardiac and Pulmonary Care of Cancer Patients

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Lockdrawer WJM-2

An added complication... in the treatment of bacterial bronchitis*

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary.
Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Precautions: If an allergic reaction to cefaclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such a condition, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Usage in Pregnancy—Although no teratogenic or antifertility effects were seen in reproduction studies in mice and rats receiving up to 12 times the maximum human dose or in ferrets given three times the maximum human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus

Usage in Infancy—Safety of this product for use in infants less than one month of age has not been established

Adverse Reactions: Adverse effects considered related to cefaclor therapy are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70) and nausea and vomiting (1 in 90).

As with other broad-spectrum antibiotics, colitis, including rare instances of pseudomembranous colitis, has been reported in conjunction with therapy with Ceclor

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 1[illegible]). Pruritus, urticaria, and positive Coombs tests each occur in l[illegible] than 1 in 200 patients. Cases of serum-sickness-like reactio[illegible] (erythema multiforme or the above skin manifestations accompa[illegible] by arthritis/arthralgia and, frequently, fever) have been report[illegible]. These reactions are apparently due to hypersensitivity and ha[illegible] usually occurred during or following a second course of thera[illegible] with Ceclor® (cefaclor). Such reactions have been reported m[illegible] frequently in children than in adults. Signs and symptoms usu[illegible] occur a few days after initiation of therapy and subside withi[illegible] few days after cessation of therapy. No serious sequelae hav[illegible] been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which ha[illegible] occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosino[illegible] (1 in 50 patients) and genital pruritus or vaginitis (less than 1 [illegible] 100 patients).

Causal Relationship Uncertain—Transitory abnormalities i[illegible] clinical laboratory test results have been reported. Although t[illegible] were of uncertain etiology, they are listed below to serve as alert[illegible] information for the physician.

Hepatic—Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less [illegible] 1 in 500) or abnormal urinalysis (less than 1 in 200). (100)

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor is contraindicated in patients with known allerg[illegible] the cephalosporins and should be given cautiously to penicil[illegible] allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophyla[illegible] of rheumatic fever. See prescribing information.

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Lilly

Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285.

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The Western
Journal of Medicine

The Tip of a Huge Iceberg?

This special issue is devoted to what is generally called occupational medicine. It has been prepared by a young but already distinguished investigator and teacher in this field. Taken together, the articles offer a diverse and yet comprehensive view of the subject, and the editors and readers of the journal are indebted to Dr. Charles E. Becker for preparing this important contribution to the general medical literature.

But one senses that the health care problems discussed in these papers may represent only the tip of a huge iceberg of problems—problems that will occupy medical research, teaching and patient care for many decades to come, in much the same way that infectious diseases dominated the scene in decades gone by, recently having been somewhat displaced by the relative dominance of what we call chronic diseases. The former were diseases of invasion of the body by living microbes of one kind or another, and the latter are more likely diseases generated from within the body by the genes, disturbances of metabolism and the inherent processes of aging. But the diseases referred to as occupational are different. They are caused by our own activities working in an industrialized society in an endeavor to improve our standard of living and quality of life. In a real sense these might be called *humanogenic diseases*—that is, illnesses that are caused by the work or industrial activities of us modern day humans.

These man-caused or humanogenic illnesses that are occurring in our industrialized society are apt to be identified first in or near the workplace as is shown in many of the articles to be found in this issue. But many of them spread to the families of workers or to the environment, and some of the etiologic agents of these diseases have actually spread so far as to be found in the crust of the earth, the waters of the seas and the gases of the atmosphere, and even as persistent constituents of biological food chains. They are fast becoming agents of at least potential diseases not only in the workplace but also as contaminants of the closed biosphere in which we all must live.

But it is in the workplace and its environs that these illnesses are the most concentrated and therefore often best studied. Sometimes the effects are manifest as acute illness or injury and are usually relatively short-lived, in which case the cause and effect are easier to determine. More often, as is pointed out in many of the papers in this issue, there is a substantial lag time between exposure to the cause, development of the illness, subsequent diagnosis and eventual treatment. In passing, it is noteworthy that this lag time is usually shortest with infectious diseases, apt to be longer in the course of chronic illnesses, but it may be many decades before the ill effects of an occupational exposure become evident. The methods to study diseases that occur in such prolonged dimensions of time are still primitive and largely unproved. New epidemiologic approaches are being tried, as is extrapolation from laboratory and animal studies to the illness in humans. The prospective, statistically significant, double-blind studies are difficult, costly and often simply impossible for study of these diseases. New and better investigational methods are urgently needed and no doubt will be developed.

Because in the final analysis these diseases are caused by humans, the potential impact of this upon our already overly litigious society could become a destructive if not actually an overpowering social phenomenon. Already one well-known industrial corporation, reported to be soundly managed and solvent, has sought relief in bankruptcy because of the number of legal actions brought against it by or in behalf of workers exposed to asbestos fibers which were not known to be a serious health hazard at the time of their exposure. If this be a bellwether sign, one may wonder how well our social system, and even our legal system, will be able to cope, both to prevent as yet unknown and undiagnosed man-made illnesses and also to deal with their untoward effects. Issues of *who* is to be responsible for *what* are clearly involved as well as is the health of our industrialized society itself.

Medicine has always been part of the fabric of the society it serves. Each major advance weaves it in more closely. In our society the conquest of the major infectious diseases, the current efforts to control chronic disease and now the problems of the humanogenic illnesses only just looming on the horizon—all have had, are having and will have enormous social, economic and political consequences. The workplace is a microcosm or testing ground for what in larger dimensions become the problems of an industrialized society and the closed biosphere. There is need for new methods of study. More accurate methods of measurement must be found. A better social approach to illness engendered by an industrialized society, whether in a workplace, its environs or within the closed biosphere itself is needed. Just how all this is to be done is not yet clear.

The editors hope that this special issue of *WJM* gives at least a glimpse of what will surely be a major new dimension of medicine. Occupational medicine, as we know it today, seems to be only at the tip of what may well turn out to be a huge iceberg of problems. —MSMW

Occupational Medicine — Long History and Bright Future

SPECIAL SYMPOSIUM EDITOR
CHARLES E. BECKER, MD

. . . when a doctor arrives to attend some patient of the working class he ought not to feel his pulse the moment he enters, as is nearly always done without regard to the circumstances of the man who lies sick. . . . For so runs the oracle of an inspired teacher: "When you come to the patient's home, you should ask him what sort of pains he has, what caused them, how many days he has been ill, whether the bowels are working and what sort of food he eats." So says Hippocrates. . . . I may venture to add one more question: What occupation does he follow?

BERNARDINO RAMAZZINI
Diseases of Workers, 1713[1]

Occupational medicine is a medical specialty with a long history and a bright future. Like medical specialties, such as infectious diseases and oncology, occupational medicine has its roots in a broad scientific discipline in which there is need for a focused attention. This focused attention is on the growing scientific body of information concerning the relation of health to one's work and environment. As with other topics covered in earlier special issues of THE WESTERN JOURNAL OF MEDICINE devoted to geriatric medicine, health care costs and nutrition, occupational medicine often falls between the cracks of growing knowledge and busy practice.

The goal of this special symposium is to emphasize that a knowledge of occupational medicine is important to all practitioners. Occupational medicine is defined as "that branch of medicine that deals with the relationship of man to his occupation for the purpose of the prevention of disease and injury and promotion of optimal health and productivity and social adjustment."[2] To fulfill this broad goal occupational medicine builds on a framework of general medicine and adds three areas of expertise—industrial hygiene, epidemiology and toxicology.

The term "industrial medicine" originated when physicians were employed in large industrial settings to provide general medical and surgical care. "Occupational medicine" is a broader term encompassing the effects of our growing technological society, increased longevity and the recognition of long latency periods for diseases caused by environmental and workplace exposures. For many years occupational medicine was isolated from the mainstream of medical care and medical education. Training programs were often located in schools of public health which may have had difficulty integrating their educational activities with clinical training programs of affiliated medical schools.

Medical practitioners have identified mounting problems from chemical contamination that extend from the workplace into the community.[3] Examples include the Love Canal; polychlorinated biphenyls in Japan; dioxin in Seveso, Italy; mercury contamination in Minamata Bay; lead pollution in cities and around smelting plants; nervous system, liver and reproductive toxicity from chlordecone (Kepone) in Virginia, and male sterility from dibromochloropropane (DBCP) in California. These events give rise to important political, social and economic considerations that emphasize the need for specialized training in occupational medicine.

How large are workplace and environmental health problems and who is being trained to deal with them? Most of the 105 million workers in the United States do not have easy access to occupational medical services. Estimates compiled by various governmental agencies suggest that there are approximately 10 million workers seeking care for occupational diseases, and almost 400,000 new cases of occupational disease per year.[4] In 1979 California reported that approximately 11 percent of the work force had occupational injury or illness. The impact on health from air, water and soil pollution is difficult to estimate and may be obscured by the length of time between exposure and onset of illness. To face the challenge of diagnosing and preventing these disorders there are only 5,000 to 10,000 physicians in the United States who identify themselves as working primarily in occupational medicine. Approximately 10 percent are certified by the American Board of Preventive Medicine in the field of occupational medicine.

The responsibility for assessing occupational and environmental health problems often falls on the shoulders of primary care physicians or emergency room personnel with limited knowledge and training in occupational medical sciences. New technologies of energy production, space travel, bioengineering and microelectronics

create a reservoir of new and potentially unrecognized health hazards. Basic and clinical research in the workplace is made difficult by concern for patent protection and other complex legal issues. Competing interests of workers, unions, employers and government may stifle logical scientific investigation of the health consequences of workplace and environmental exposures.

There have been occasional real or perceived problems regarding the loyalty of physicians hired by industry to occupational health care patients.[5] In July 1976 the American Occupational Medical Association developed a code of ethical conduct for physicians practicing occupational medicine. The code spells out in detail 12 guidelines for physicians providing occupational medical services. This is a unique achievement in that it established a specialized ethical code for a group of physicians practicing a specialty. It is important to recognize that nonoccupational physicians acting as occupational physicians in primary care practice or emergency medicine must also be guided by this code of ethics.[6]

Primary care physicians also must have a high index of suspicion for occupational diseases, inquiring about the temporal relationship of the illness to the occupation and inquiring whether any other workers have been similarly affected. Because occupational and environmental diseases frequently masquerade as routine medical or surgical disorders the work history must include a thorough occupational history,[7] including all previous employment, duration on a single job and reasons for terminating employment. Diseases with long latency, such as asbestosis, should be specifically emphasized in the work history. In addition, leisure and other nonoccupational activities can involve exposures that may complicate the work history. Specific knowledge of medical surveillance on the job and data from environmental monitoring (such as lead or cholinesterase) should be obtained by the examining physician. Finally, primary care physicians seeing occupational cases should maintain appropriate lines of referral in their community so that expertise in occupational and environmental issues is readily available.

With a growing scientific literature in the field of occupational medicine, primary care physicians may now readily obtain continuing education in the specialty. This special issue of the journal by no means provides a complete listing of the basic scientific information required in occupational medicine, but it does provide a background on which to build future continuing education in this field.

Seven articles in this issue discuss specific organ pathology: Dr. Sheppard focuses on the lungs; Drs. Mathias and Maibach, the skin; Drs. Lotti, Becker and Aminoff, the nervous system; Dr. Dobie, the ears; Dr. Pond, the liver; Drs. DeBusk and Dennis, the cardiovascular system, and Dr. Whorton, the reproductive system. Four papers deal with unique topics in occupational medicine: Dr. LaDou reviews the health effects of shift work; Dr. Landrigan, toxic metals; Dr. Goldman, radiation, and Drs. Rom and Lockey, a unique cancer in the workplace. The three basic disciplines of occupational medicine are covered specifically: Drs. Peters, Wright and Garabrant review *epidemiology;* Dr. Hooper, risk assessment in *toxicology,* and Drs. Rappaport, Spear and Yager, *industrial hygiene.* Next, Dr. Wade reviews the history of occupational medicine and explores the role of government. The final article gives the key elements of an occupational history for general physicians.

As continuing medical education is necessary and vital for all physicians, the responsible provision of new information to those who have a "right to know" is a key factor in the obligation and the challenge for physicians in occupational medicine. Workers, management and the public must increase their knowledge about occupational and environmental hazards.[8] Physicians trained in occupational medicine can meet this need with objective information presented in a clear, caring fashion.

Occupational medicine is entering the mainstream of medical education, research and teaching. It is a versatile, challenging, multidisciplinary specialty with a strong international flavor and a broad scope. Occupational medicine strikes a delicate balance between the individual worker as patient, her or his employer, unions, government and society. The physician with expertise and interest in this vital area stresses prevention of disease through a solid scientific background and applied knowledge of industrial hygiene, epidemiology and toxicology.

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Occupational Asthma

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Bronchospasm is a common cause of morbidity in the workplace. More than 100 agents are now recognized as occupational causes of asthma and numerous agents can cause exacerbations of preexisting asthma. Because of the large number of potential causative agents and the complexity of modern industrial processes, knowledge of the characteristic clinical features of occupational asthma is the key to recognizing this disease. Early diagnosis of occupational asthma is important in preventing long-term morbidity. Present evidence that prolonged exposure to some work-encountered agents can cause asthma that persists for years after the end of exposure suggests that avoidance is the only acceptable countermeasure against this disease.

Occupational asthma usually is defined as reversible airways obstruction caused by workplace exposure in a previously healthy person. Although an association between asthma and workplace exposure was first suggested more than 250 years ago,[1] the actual incidence and prevalence of this disease remain unknown. Numerous recent reports of specific occupational causes of asthma point to well over 100 causative agents (Table 1).[2,3]

Some commonly encountered agents, such as toluene diisocyanate (TDI), grain dust and the dust of western red cedar, cause asthma in 5 percent or more of exposed workers.[4-6] These observations suggest that occupational asthma is a relatively common disease.

The significance of workplace exposure in causing reversible airways obstruction is not limited to previously healthy persons in whom asthma develops solely from workplace exposure. Asthma is an extremely common disease, affecting an estimated 3 percent to 10 percent of the adult population of the United States.[7,8] Many people with asthma have mild disease and can function perfectly normally under most circumstances. As a result, every common occupation includes a significant number of workers with asthma. Many agents encountered in the workplace that have little or no effect on nonasthmatic workers can cause pronounced symptomatic bronchoconstriction in workers with asthma. Thus, in addition to causing new asthma in previously healthy people, workplace exposure is an important cause of exacerbations of preexisting asthma.

In this review I will discuss the pathophysiology, clinical features, diagnosis and treatment of both new-onset asthma caused by occupational exposure and preexisting asthma made worse by work-encountered agents.

Exacerbations of Preexisting Asthma

Extreme sensitivity of the airways to physical, chemical and pharmacologic stimuli is a characteristic feature of asthma.[9,10] In people with asthma, therefore, a greater degree of bronchoconstriction develops in response to a wide variety of stimuli than in people with no pulmonary abnormalities. Recent studies suggested that this feature of asthma, called nonspecific bronchial hyperresponsiveness,[10] may explain many of the diverse causes of exacerbations of asthma.

Although the precise cause of this bronchial hyperresponsiveness is unknown, many of the stimuli that can produce bronchoconstriction in people with asthma do so at least in part by stimulating activity in the parasympathetic nerves of the airways. Thus, the bronchoconstriction induced by cigarette smoke,[11] sulfur dioxide,[12,13] cold air[14,15] and inert dust[16] can all be inhibited by treatment with atropine. These agents probably initiate exacerbations of asthma by stimulating airway afferent nerve fibers that are strategically located just below the tight junctions between adjacent airway epithelial cells. The location of these nerve endings in

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close proximity to the airway lumen and in large numbers in the larynx and trachea and near the bifurcation of large airways[17] makes them particularly susceptible to stimulation by inhaled particles and water-soluble gases. Thus, a number of agents encountered in the workplace can potentially cause exacerbation of asthma by this mechanism.

Irritant Gases

Although hundreds of gases that can potentially irritate mucous membranes are commonly encountered in industry, little or nothing is known about the effects of most of them on airway function in people with asthma. Because regulatory standards for workplace exposure, unlike air pollution standards, are generally not designed to protect the most sensitive persons, allowable concentrations of irritant gases may be orders of magnitude higher than the concentrations needed to cause exacerbations of asthma. One example of this phenomenon is sulfur dioxide, a highly water-soluble gas encountered in significant concentration in the workplace for approximately 500,000 workers in the United States.[18] On the basis of data showing little effect on people with no pulmonary abnormalities of sulfur dioxide in concentrations less than 5 ppm, the present Occupational Safety and Health Administration threshold limit value for the gas allows exposure to an average concentration of 5 ppm over an eight-hour work shift.[18] This standard allows brief exposure to significantly higher concentrations as long as the eight-hour average does not exceed 5 ppm. Recent studies, however, showed that in persons with mild asthma pronounced symptomatic bronchoconstriction can develop after five minutes of breathing concentrations of sulfur dioxide of 0.5 ppm or less.[19-21] It is therefore clear that workplace exposure to sulfur dioxide can cause exacerbations of asthma despite airborne concentrations well below those allowed by present federal standards.

Unfortunately, little is known about the precise mechanism by which gases such as sulfur dioxide stimulate activity in airway afferent nerves, so it is not presently possible to predict which of the hundreds of other commonly used gases, dusts and fumes will produce similar effects and at what concentration these effects will occur. Nonetheless, it seems likely that exposure to irritant gases, dusts and fumes is an important cause of work-related exacerbations of asthma.

Allergens

Inhalation of specific allergens is a well-recognized cause of exacerbation of asthma. Allergen inhalation not only causes acute and delayed bronchoconstriction, but it can also lead to an increase in nonspecific bronchial hyperresponsiveness[22] and may thus increase the overall clinical severity of asthma. Specific allergy is probably an important mechanism of new onset asthma caused by work and will be discussed subsequently, but it is also an important cause of work-associated exacerbations of preexisting asthma. Animal proteins, encountered by laboratory workers, veterinarians and farmers, are examples of allergens that have been im-

TABLE 1.—*Causes of Occupational Asthma (Partial List)*

Material	*Industry or Occupation at Risk*
CHEMICALS (general)	
Isocyanates	
Toluene diisocyanate	Polyurethane, insulators, laminators
Diphenylmethane diisocyanate	Laminators, polyurethane foam
Hexamethylene diisocyanate	Painters, plastics
Naphthalene diisocyanate	Chemists, rubber workers
Anhydrides	
Trimellitic anhydride	Chemical workers
Phthalic anhydride	Paint, plastics
Hexahydrophthalic anhydride	Epoxy resins
Tetrachlorophthalic anhydride	Epoxy resins
Polyvinyl chloride vapor	Meat wrappers
METALS	
Chromic acid	Chrome platers, welders
Potassium chromate and dichromate	Chrome workers, cement workers
Platinum salts	Platinum refiners
Chloroplatinic acid	Platinum refiners, chemists
Nickel sulfate	Nickel platers, welders
Nickel carboxyl	Chemical workers, nickel platers, welders
Vanadium	Boiler cleaners, turbine cleaners
Aluminum?	Aluminum, pot-room workers
DYES	
Anthraquinone	Fabric dyeing
Carmine	Cosmetics, dyes
Paraphenyl diamine	Fur dyeing
Hexafix brilliant yellow	Dye manufacturers
Drimaren brilliant blue	Dye manufacturers
Cibachrome brilliant scarlet	Dye manufacturers
Henna extract	Beauticians
FLUXES	
Colophony (soft-core solder)	Solderers, electronics workers
Aminoethylethanolamine	Aluminum soldering
DRUGS	
Benzyl penicillin	Pharmaceuticals
Ampicillin	Pharmaceuticals
Sulfathiazole	Pharmaceuticals
Tetracycline	Pharmaceuticals
Psyllium	Pharmaceuticals
Methyldopa	Pharmaceuticals
Salbutamol	Pharmaceuticals
Piperazine dihydrochloride	Pharmaceuticals
Chloramine T	Pharmaceuticals, laboratory workers
Organophosphates	Farm workers, pesticide formulators, fumigators
ENZYMES	
Pancreatic extracts	Pharmaceutical workers
Bacillus subtilis	Detergent manufacturers
Papain	Food processors
Trypsin	Plastics and rubber workers
Flaviastase	Pharmaceutical workers

TABLE 1.—*Causes of Occupational Asthma (Partial List) (continued)*

Material	*Industry or Occupation at Risk*
Bromelain	Food processors
Pectinase	Food processors
MISCELLANEOUS CHEMICALS	
Formaldehyde	Laboratory workers, embalmers, insulators, textile workers
Dimethylethanolamine	Paint sprayers
Ethylenediamine	Rubber workers, photographic processors
Persulfate salts	Chemical workers, beauticians
Ethylene oxide	Medical sterilizers
Pyrethrin	Fumigators
Ammonium thioglycolate	Beauticians
Monoethanolamine	Beauticians
Hexamethylenamine	Beauticians
ANIMALS	
Domestic animals	Farmers, veterinarians, meat processors
Birds	Poultry breeders, bird fanciers
Bats, mice, guinea pigs	Laboratory workers
Sea squirt	Oyster farmers
Fish (glue)	Bookbinders, postal workers
Silkworms	Silk sericulturers
Grain mites, weevils	Grain mill and storage workers, bakers
Prawns	Processors
Crabs	Processors
PLANTS	
Wheat	Farmers, grain handlers
Buckwheat	Bakers
Grain dust	Farmers, grain handlers, bakers
Rye flour	Bakers
Hops	Brewers
Tamarind seeds	Millers, spice processors
Castor beans	Farmers, castor bean workers
Coffee beans	Farmers, coffee bean workers
Wool	Textile workers
Tobacco dust	Cigarette manufacturers
Tea	Food processors
Cotton, flax, hemp	Textile workers
VEGETABLE GUMS	
Acacia	Printing
Tragacanth	Printing, food processing
Karaya	Food processing
Arabic	Printing
WOOD DUSTS	
Western red cedar	Woodworkers
Cedar of Lebanon	Woodworkers
Mahogany	Woodworkers
California redwood	Woodworkers
Oak	Woodworkers
Iroko	Woodworkers
Boxwood	Woodworkers
Cocabolla	Woodworkers
Zebrawood	Woodworkers
Mansonia	Woodworkers
Mulberry	Woodworkers

plicated both in exacerbations of asthma and in causing new-onset asthma.[23]

Many other agents that may be encountered primarily in the workplace are important causes of exacerbation of asthma—including viral upper respiratory infections (an occupational risk for teachers and day-care workers)—work-associated stress and heavy exercise in cold or dry air, but these are beyond the scope of this review.

New-Onset Asthma Caused by Work

A long (and growing) list of materials have now been associated with the new-onset of asthma in exposed workers (Table 1). When tests of nonspecific bronchomotor responsiveness have been carried out, most affected workers have exhibited abnormally intense bronchoconstriction to histamine, methacholine and cold air.[5,6,24-28] Furthermore, when these workers are able to avoid the responsible agent, bronchomotor responsiveness often improves in parallel with other signs of clinical improvement and sometimes returns to normal within a period of months to years.[24,27] However, a long-term exposure and a long duration of symptoms before cessation of exposure increase the likelihood that an affected worker will continue to have asthma even after leaving the workplace.[27] This evidence suggests that work-induced asthma may result from ongoing injury to airways due to repeated and continuing exposure to causative agents.

The mechanisms by which specific agents injure airways leading to the development of asthma are largely unknown. For some agents (such as green coffee beans[29] and phthalic anhydride[30]), the presence of specific IgE antibodies strongly implicates an immunologic mechanism. Furthermore, the fact that other agents, such as TDI, can cause bronchoconstriction in affected workers but not in nonaffected asthmatic subjects at extremely low concentrations[6,31] also suggests an immunologic mechanism. The failure thus far to find a specific antibody in most workers with TDI-induced asthma may be due to failure to identify the appropriate antigen because TDI can react avidly with numerous tissue proteins. Even if an immunologic mechanism is involved in inducing bronchoconstriction, the mechanisms by which these agents cause immunization and ongoing damage to airways remain speculative.

Clinical Presentation

When a worker complains of wheezing and chest tightness occurring primarily at work with improvement during weekends and vacations, most physicians correctly suspect the presence of work-associated asthma. Unfortunately, there are several common variations to this classic presentation that can make the physician's task more difficult. Although in many workers symptoms of bronchospasm develop immediately after exposure to the responsible agent, these symptoms are often minor or may be entirely absent, although more pronounced bronchoconstriction commonly occurs 4 to 12 hours later. This pattern, called the late asthmatic response, is shown in Figure 1 and may manifest with symptoms of bronchospasm occurring primarily in the

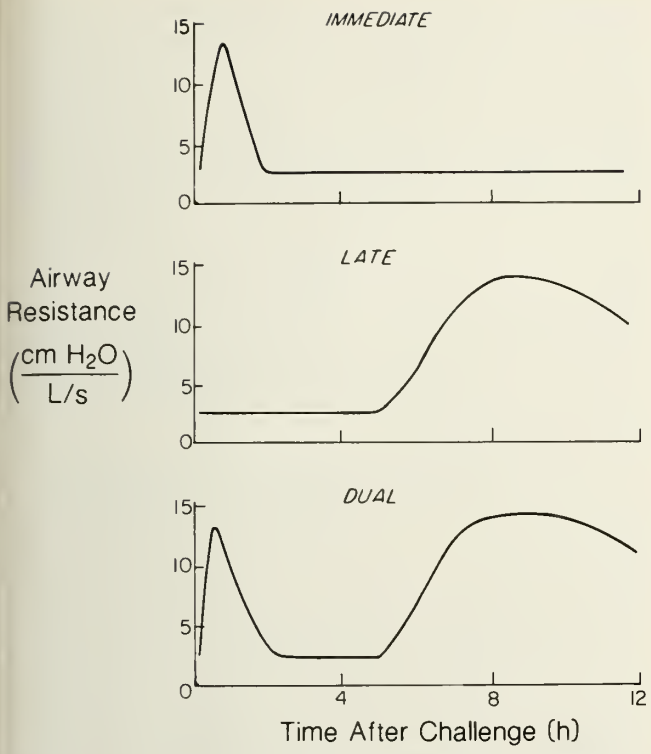

Figure 1.—Temporal patterns of increased airways resistance after exposure to agents that cause occupational asthma.

evenings or on awakening. A dual response, also shown in Figure 1, manifests with symptoms at work that abate and then recur after the end of exposure. Late and dual responses occur more commonly than simple immediate responses in some forms of work-induced asthma. For example, these patterns occur in up to 80 percent of workers with asthma caused by the dust of western red cedar.[32] Occasionally, a single exposure to the offending agent can cause repeated episodes of bronchospasm over several days.

Although wheezing is the most widely recognized symptom of asthma, many workers initially complain primarily of a cough that may or may not be productive.[29,32,33] Because coughing is often the earliest symptom of asthma, recognition of this symptom may be important in early diagnosis. Recent evidence suggests that asthma initially caused by workplace exposure can persist for many years after exposure ceases and that the likelihood of persistent asthma increases with an increased duration of symptoms.[27] Early diagnosis may thus be important in preventing long-term morbidity.

As in nonoccupational asthma, rhinitis is commonly associated with work-induced asthma and may precede the onset of asthma by months to years. Because cough and rhinitis are both common symptoms of other disorders (such as viral upper respiratory infections and bronchitis), their significance is often overlooked.

Another important and often unrecognized feature of work-induced asthma is that the disease usually does not develop for months to years after onset of exposure. In fact, for many agents the incidence of asthma increases with the duration of exposure. Thus, in one study of bakers with grain-induced asthma, the mean duration of exposure in affected workers was 17.1 years.[5]

Etiologic Agents

Table 1 lists some of the agents that have been found to cause work-induced asthma. Several additional agents are described each year, and many new causative agents are undoubtedly introduced into the workplace each year. The following examples of agents that commonly cause asthma illustrate important features of work-induced asthma.

Western Red Cedar

Inhalation of wood dust is a common cause of asthma among carpenters and sawmill workers. The best studied causative agent is the dust of western red cedar *(Thuja plicata),* which has been reported to cause asthma in 5 percent to 24 percent of exposed workers.[4,24,27,32,34] The causative agent in western red cedar appears to be plicatic acid because the inhalation of this chemical causes the same pattern of bronchospasm in affected workers as does inhalation of crude dust. As with a number of other types of work-induced asthma, most affected workers have no history of atopy and skin test reactivity, and the presence of specific antibodies has not been well correlated with the development of asthma.[24,32] Long-term follow-up of affected workers has shown that in as many as 50 percent, symptoms of asthma and nonspecific bronchial hyperresponsiveness may not improve even after several years away from the offending agent.[27]

TDI

Toluene diisocyanate is one of a growing list of highly reactive low-molecular weight chemicals that can cause work-induced asthma. Like western red cedar, TDI causes asthma in about 5 percent of exposed workers. Toluene diisocyanate in high concentrations produces acute inflammation of the airways in animals experimentally and is quite irritating to all people exposed to it,[6,29] but the concentrations required to cause bronchoconstriction in some sensitized workers (less than 0.001 ppm) are orders of magnitude lower. Although TDI acts as a β-adrenergic antagonist when added to cultured lymphocytes,[35] this feature is unlikely to explain TDI-induced asthma because more potent β-antagonists such as propranolol do not cause asthma in healthy people. The observation that affected workers have often been exposed to frequent accidental spills of the chemical suggests that acute damage to airways may somehow contribute to the development of asthma, but a precise mechanism has not yet been identified. Like a number of other low-molecular weight molecules that cause asthma (for example, phthalic anhydride and trimellitic anhydride), TDI is highly chemically reactive, and its irritant properties are thought to be caused by its ability to denature tissue proteins. These chemicals, which are too small to act as antigens themselves, may damage airway cellular proteins and thus secondarily lead to immunologic sensitization to complexes of the chemical and endogenous proteins or to the altered protein itself.[36-38] Toluene diisocyanate, a major component of

polyurethane, is widely used in industry and is commonly only one of a large number of chemicals used in a given production process. As such, identification of TDI as the agent responsible for asthma in an individual worker often requires a well-informed worker, a careful history, and/or a workplace air sampling.

The widespread use of TDI has led to the recognition of TDI-induced asthma in people who never worked directly with the chemical. One such episode involved a group of office workers exposed to TDI from their office ventilation system, the intake of which was near the exhaust from an adjacent TDI factory.[39] In addition, individual cases of TDI-induced asthma have been identified in people who encountered the material from home use of polyurethane foam.[40]

Cotton Dust

Exposure to raw cotton, flax and hemp has long been recognized as a cause of acute cough, chest tightness and wheezing.[41-44] This symptom complex, which has been called byssinosis, can be reproduced by inhalation of an extract of the cotton bract, but the component of the cotton bract that is responsible for these symptoms has not been identified. The disease differs from other forms of work-induced asthma in several respects. Whereas other forms of asthma tend to recur throughout the work week so that pulmonary function is generally worst at the end of the week, byssinosis characteristically causes prominent symptoms on returning to work after an absence. These symptoms decrease on successive consecutive work days. In addition, the time course of bronchoconstriction is unusual in byssinosis, generally increasing gradually within a few hours after the onset of exposure. Furthermore, the attack rate is quite high, sometimes affecting more than 50 percent of heavily exposed workers.[44,45] These features suggest that the mechanism of bronchoconstriction in byssinosis may be different from that involved in other forms of work-induced asthma. Some researchers have suggested that cotton bract causes bronchoconstriction by directly stimulating airway mast cells to release histamine because cotton bract extract has been shown to cause release of histamine from human lung tissue in vitro.[46,47] Recent evidence suggests that bract extract may also directly stimulate airway smooth muscle to contract.[48]

Diagnosis

The most important tool in establishing a diagnosis of work-associated asthma is a careful occupational history. The development of cough, rhinitis or wheezing (or combinations of these) since the onset of employment, especially if the symptom began after a delay of months to years, should suggest the diagnosis. A history of increased symptoms while at work or within several hours after a work shift provides important confirmation. Clear-cut improvement during weekends or holidays may not occur, but if present, strongly suggests the diagnosis. A detailed list of materials encountered in the workplace and in the home workshop may identify a known cause of asthma.

Physical examination may show wheezing but usually does not find any pulmonary abnormalities. Spirometry carried out before and after a work shift can be diagnostic but is insensitive and, if only done once, may not yield abnormal results in a significant percentage of affected workers. Measurement of peak expiratory flow with a portable peak flowmeter, preferably at hourly intervals every day (including weekends) for two weeks, can be quite helpful in establishing the presence of asthma (suggested by a repeated difference of more than 20 percent between maximal and minimal values on a given day) and the temporal relationship between airways obstruction and work.[49,50] The major shortcoming of this measurement is its dependence on patient effort and cooperation.

Work-induced asthma, like other forms of asthma, is associated with increased nonspecific bronchial hyperresponsiveness.[5,6,24-27] Measurement of bronchial responsiveness by obtaining dose-response curves to inhaled cholinergic agonists or histamine is thus often useful in providing further confirmation of the diagnosis. Although these tests do not distinguish work-induced asthma from other forms of asthma, in workers with a strongly suggestive history the finding of increased bronchial responsiveness is often sufficient to confirm the diagnosis. Normal nonspecific airway responsiveness, however, does not rule out the presence of work-related asthma.[31,51]

When, despite these other investigations, the diagnosis still remains in doubt or when an agent not previously known to cause asthma is suspected, specific inhalation challenge testing with the suspected agent may be definitive. Specific challenge testing is often complicated by a lack of precise information about the likely responsible agent and the dose required to cause bronchoconstriction, or both. As a result, except for workers clearly exposed to only one material in the workplace (a rare occurrence), in the presence of a suggestive history, negative results should be interpreted with caution. Because of the common occurrence of late responses, patients undergoing inhalation challenge studies must be observed for at least 8 to 12 hours after challenge. To be valid, these tests must include appropriate control studies and ideally should include exposure on separate days to different doses of the suspected agent.

Treatment

Despite all the evaluations just suggested, it is often not possible to determine with certainty whether an individual worker has asthma specifically caused by an agent encountered in the workplace or has preexisting but quiescent asthma exacerbated by workplace exposure. Fortunately, it is often not necessary to make this distinction because the treatment—avoidance of the offending agent (or agents)—is the same for both conditions. In the case of specific allergens, this usually requires changing to a different workplace entirely because extremely low doses may cause profound bronchoconstriction.

When the worker cannot or will not change his or her

job, usually for financial reasons, treatment with standard bronchodilators may provide symptomatic relief and treatment with cromolyn is often effective in preventing acute episodes of bronchoconstriction. However, because prolonged exposure to at least some offending agents can lead to persistent asthma even after leaving the workplace,[27] symptomatic therapy is generally not recommended.

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Perspectives in Occupational Dermatology

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Because large surface areas of the skin are exposed directly to the environment, skin is an organ particularly vulnerable to occupationally induced disease. Statistics show that, excluding accidental injury, nearly half of all occupational illnesses occur in this organ; a fourth of all workers suffering from occupational skin disease lose an average of 10 to 12 workdays. The constant evolution of new industrial chemicals and methods of manufacture continue to bring new skin hazards and disease into the workplace. Occupational health physicians and practitioners, who usually have minimal training in dermatology, must diagnose and treat unfamiliar diseases in a setting of even less familiar, often overwhelming, technology. A thorough understanding of cutaneous defense mechanisms, clinical patterns of occupational skin disease and methods for establishing accurate diagnoses is essential.

The first record of occupational skin disease may be attributed to Celsus, who described skin ulcerations from corrosive materials in 100 AD. About 1500 AD, Paracelsus and Agricola described cutaneous ulcerations from metallic salts in miners. Little else was recorded until 1700, when Ramazzini wrote his first major treatise on disease in tradesmen. In 1775 Percival Pott published the first description of an occupationally induced neoplasm, cancer of the scrotal skin in chimney sweeps who had been in contact with soot.[1]

The first major treatise on occupational skin disease, *The Dermatergoses,* was published in 1915 by Robert Prosser White,[2] an energetic English general practitioner. The detailed clinical descriptions of occupational skin diseases in this book, particularly the description of irritant dermatitis, continue to be useful today. Publication of *The Dermatergoses* undoubtedly had some role in prompting the United States Public Health Service to study skin disease in industry, culminating in the publication of *Occupational Diseases of the Skin* by Schwartz, Tulipan and Peck in 1939.[3] The last edition of this book was published in 1957.[4] In a field undergoing frequent and dramatic technological change, recent smaller texts provide excellent but limited information on various subject areas.[5-7]

Excluding accidental injuries, which account for approximately 97 percent of occupational disease, skin disease constitutes almost 50 percent of the remaining occupational illnesses.[8] This is not surprising because the skin, with its large surface area in direct contact with the environment, is one of the most vulnerable organ systems. Approximately one of every four workers afflicted with occupational skin disease loses time from work, an average of 10 to 12 days.[8] This represents an enormous loss of productivity each year. The highest relative risk occurs in the manufacturing and agricultural industries, where workers are four times more likely to have occupational skin disease than in other industries.[8]

Cutaneous Defense Mechanisms

The skin is endowed with a host of versatile mechanisms to defend itself against environmental and occupational insults and stresses. These include a barrier to shield against penetration by chemical substances and prevent fluid loss from the body, buffering action, immunologic defense mechanisms, resistance to mechanical friction and trauma, cooling mechanisms to reduce thermal stress, protection against solar radiation and defense against attack by microbial agents.[9]

The Cutaneous Barrier

The cutaneous barrier may be considered from anatomical, biochemical and physiological viewpoints.[10]

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Since the classic water loss experiments of Windsor and Burch almost 40 years ago,[11] it has been recognized that the principal barrier to percutaneous penetration resides in the outermost layer of skin, the stratum corneum. This 15- to 30-μm layer consists of flat, hexagonal cells, containing keratin and other structural proteins. It covers most body areas; its depth varies with the body regions. It is only a few cells thick over eyelid and genital skin, but approaches 300 μm on the palms and soles. The intercellular spaces are filled with a nonpolar lipid material, and may be the principal route of penetration for some substances.[12] Damage or removal of the stratum corneum significantly enhances permeability to a variety of penetrants.[10] The protective function of this anatomic barrier may be further subserved by the eccrine sweat glands, the activity of which may wash off and dilute any noxious substances that come in contact with the skin.

Biochemically, 50 percent to 60 percent of the stratum corneum is structural cytoplasmic protein, 20 percent to 25 percent water and 15 percent to 20 percent lipid. Changes in the water content through entrapment of water on the skin surface or prevention of evaporation (hydration), or environmental chapping (dehydration), may dramatically increase permeability. Alteration in protein or lipid content through detergent or solvent action may produce a similar effect. Qualitative changes in cutaneous lipids may further alter cutaneous permeability. Diets deficient in essential fatty acids produce scaling of the skin associated with pronounced increases in transepidermal water loss.[13]

The physiological basis for percutaneous penetration has been most frequently expressed in the equation known as Fick's law:

$$J = (DK/\lambda)\Delta C$$

in which J equals flux of the penetrating molecule, D represents the diffusibility of the penetrating molecule in the stratum corneum, K represents the partition coefficient (that is, the ratio of the solubility of a substance in the stratum corneum to its solubility in the applied vehicle), λ equals thickness of stratum corneum, and ΔC equals concentration difference of the penetrating molecule across the stratum corneum.[10] While the mathematical laws governing penetration are in reality more complex, the above relationships are useful in understanding and predicting qualitative changes in penetration. Changes within the stratum corneum that enhance diffusibility, vehicles for penetrating molecules that result in increased solubility in the stratum corneum relative to the vehicle, cutaneous exposures on surfaces where the stratum corneum is thinnest and increased concentrations of the penetrant may all enhance absorption over a finite period of exposure. These considerations become important when a physician is evaluating occupational exposures associated with cutaneous or systemic signs and symptoms.

Buffering Action

The skin offers some protection against exposure to alkaline substances by virtue of the buffering action of the outermost layer, sometimes called the "acid mantle." Lactic acid, amphoteric amines and weak bases are deposited on the surface, either through breakdown of the superficial cell layer or by eccrine sweat. Diffusion of carbon dioxide through the skin may further enhance the buffering action.

Immunologic Mechanisms

Immunologic defense mechanisms allow the body to react defensively to chemical stimuli, potential carcinogens and infectious agents. Both immediate (humoral) and delayed (cellular) immunity may be involved. The activities of the immune system, while normally protective, occasionally may have deleterious cutaneous effects.

Immunologic urticaria (hives) results when IgE-coated cutaneous mast cells release histamine and other vasoactive substances, following combination with the appropriate antigen. Occupationally induced urticaria is usually a secondary reaction to inhaling antigen,[14] and is often associated with other symptoms of inhalant allergy. Localized urticaria may result from direct percutaneous penetration by antigen. This phenomenon has been dubbed "contact urticaria."[15]

Delayed hypersensitivity results in a sequence of inflammatory processes collectively known as allergic contact dermatitis. Following percutaneous penetration, the antigen (hapten) must combine with a skin component (protein) before it can be recognized as antigenic. The specific carrier protein is unknown but may differ, depending upon the nature of the allergen and the individual person. Presumably, it is the hapten-protein conjugate that is ultimately recognized as antigenic. Thus, simple metallic substances such as nickel, or even low-molecular-weight lipids and carbohydrates, may occasionally cause allergic contact dermatitis. Present evidence suggests that the initial step in recognition involves selective uptake by epidermal Langerhans' cells before transport to regional lymph nodes.[16] When sensitization occurs, T cells proliferate in the paracortical areas of regional lymph nodes. Upon reexposure to antigen, these sensitized T cells release mediators (lymphokines) in the skin, resulting in inflammation. Suppressor T cells may further modulate this delayed hypersensitivity response.

Mechanical Resistance

The dermis, situated beneath a relatively thin epidermal covering, is composed chiefly of connective tissue cells and fibers as well as a matrix of ground substance. The tough fibrous and elastic components form a resilient barrier against mechanical friction and trauma, and support overlying epidermis, blood vessels, appendages and neurosensory elements. The dermis plays a prominent role in wound repair.

Cooling Mechanisms

Loss of radiant heat from the vascular bed of the skin, by virtue of mechanisms that alter blood flow in the superficial capillary network, plays an important thermoregulatory role when a person is exposed to

environmental conditions that produce skin surface temperature changes between 25 and 31° C. Above these skin surface temperatures, further thermoregulation is accomplished by evaporative cooling through activity of the eccrine sweat glands.

Protection Against Ultraviolet Radiation

The protective pigment in the skin (melanin) is synthesized in the melanocytes, located along the basal cell layer of the epidermis. The pigment is "packaged" within the melanocytes into granules called melanosomes. Under suitable stimulation from ultraviolet light, these granules are dispersed into neighboring keratinocytes, resulting in pigment darkening and enhanced protection from ultraviolet radiation. The starting point of melanin synthesis is the amino acid tyrosine, which is converted by the copper-dependent enzyme tyrosinase into dihydroxyphenylalanine (dopa). From here, melanin synthesis proceeds through a number of other intermediate steps, resulting in dopaquinone, 5,6-dihydroxyindole and indole-5,6-quinone before the final melanin polymer is formed. The melanocytes may be specifically or nonspecifically injured as a result of occupational exposures, resulting in pigmentary changes.

Microbial Defense

Intact skin is a highly resistant physical barrier to microorganisms and is infected with great difficulty. Free fatty acids, derived from enzymatic degradation of sebaceous gland lipid, may also have antifungal and antibacterial action. Odd-numbered C5, C7, C9, C11 and C13 fatty acid chains have more potent antifungal activity than even-numbered chains of the same length. Long chain unsaturated fatty acids have limited bacteriostatic activity against a small group of organisms. Once skin penetration by microorganisms has occurred, both immune and nonspecific inflammatory mechanisms provide a second line of defense.

Clinical Aspects of Occupational Skin Disease

The skin is a barrier to the systemic absorption of toxic chemicals as well as a target organ for disease.

Percutaneous Absorption

Skin absorption is an important route of entry for many substances that may produce systemic toxicity. Chemicals that are detoxified by a first pass through the liver following intestinal absorption may be more toxic when absorbed through the skin.[17] Skin absorption may be the principal route of exposure for many agricultural pesticides.[18]

Development of symptoms depends partly on the ability of a substance to penetrate through skin, as well as the inherent toxicity and quantitative degree of exposure. Any circumstance or condition of exposure in the workplace that increases percutaneous absorption may enhance toxicity. Such conditions include increases in stratum corneum hydration, particularly when substances are occluded against the skin by water-impermeable clothing (such as rubber gloves); dry, chapped skin; skin already damaged by cuts, abrasions or preexisting dermatitis; elevation of skin surface temperature, especially through heat transfer from heated industrial liquids; a favorable stratum corneum:vehicle partition coefficient, and contact with anatomical areas of skin that are more permeable (for example, eyelid, facial and genital skin).[19,20] Toxicity also depends on the total amount of exposure, which can be increased through changes in concentration of the penetrating substance and increased duration and frequency of skin contact. The interplay of the above factors on skin absorption of pesticides has been studied by Maibach and Feldmann.[21]

A partial list of substances that may produce toxic symptoms in industry following percutaneous absorption includes aniline dye (methemoglobinemia), benzidine (carcinoma of the bladder), cyanide salts (cellular asphyxia and death), organophosphates (cholinesterase inhibition, gastrointestinal, cardiovascular and neuromuscular disturbances) and other insecticides, and numerous solvents such as methyl butyl ketone (central nervous system depression and peripheral neuritis).[22] Solvents may enhance their own toxicity by damaging the stratum corneum and increasing their percutaneous absorption. Visible inflammation (dermatitis) is not a necessary prerequisite for significant percutaneous absorption. However, substances that also produce dermatitis, such as cyanide salts,[23] may enhance their own systemic toxicity.

Contact Dermatitis

Approximately 75 percent of all occupationally acquired skin disease is "contact dermatitis." This term refers to an inflammatory condition of the skin (eczema) induced by external contact between a substance or material and the skin surface. At least 80 percent of such cases are due to skin irritation; less than 20 percent are the result of contact allergy.[1]

Irritant contact dermatitis is caused by a direct, local, toxic effect and does not involve immunologic mechanisms. When effects are observed within minutes of skin contact, following a brief skin exposure with a substance such as concentrated sulfuric acid, the injury is termed a chemical burn. Most industrial irritants are relatively weak, and require frequent or prolonged skin contact before visible changes are induced. As discussed above, factors that increase the qualitative degree of exposure or enhance percutaneous penetration will increase the potential for a given substance to provoke irritant contact dermatitis. Depending on the conditions under which skin exposure occurs, almost any substance encountered in the workplace may become an irritant.[20] The most commonly encountered irritants include solvents, acids and alkalis, and soaps and detergents. Workers are usually exposed to multiple potential skin irritants, and irritation may be a cumulative result of multiple exposures. Once skin inflammation has occurred, the skin barrier is compromised and the skin becomes even more susceptible to irritation. Abrasive soaps and waterless hand cleaners (usually containing 10 percent to 20 percent petroleum distillate in a lanolin or cream formulation), are additional potential irritants.

Once irritation has occurred, these skin cleaners may do more harm than good.[24]

Allergic contact dermatitis results from immunologic mechanisms involving cellular delayed hypersensitivity. Most allergens encountered in industry are relatively weak, and require optimum circumstances of exposure in susceptible persons before sensitization occurs. This usually takes time, and months (or years) may pass before a worker actually has an allergic reaction. Thus, allergy often develops to longstanding contacts in a worker's environment, rather than recently introduced substances. Common occupational sensitizers include metal salts (nickel, chromium, cobalt, gold); rubber accelerators and antioxidants; epoxy, acrylic and phenolic resins; biocidal agents used to preserve aqueous solutions or emulsions (for example, cutting fluids), and organic dyes (such as paraphenylenediamine).[25] Domestic sensitizers (fragrances, cosmetic preservatives and topical medications) may find their way into the workplace in the form of soaps, hand creams and first aid cabinet preparations. Once allergic sensitization has occurred, only minimal quantitative exposure may be necessary to sustain dermatitis.

Photosensitivity

The activation of a chemical substance on the skin surface by ultraviolet or visible light causes a photosensitive reaction. These clinically appear as an acute sunburn or eczema on sun-exposed surfaces of the body. Phototoxic reactions are analogous to irritant contact dermatitis, and do not involve immunologic mechanisms. Polycyclic aromatic hydrocarbons, such as creosote[26] and tar, cause burning and stinging cutaneous reactions following sun exposure. Severe, bullous, phototoxic reactions occur in celery harvesters, caused by a furocoumarin liberated from celery parasitized by a common agricultural fungus ("pink rot").[27] The newer polyfunctional, ultraviolet-light-cured acrylic resins may produce phototoxic as well as photoallergic reactions.[28] Persistent photosensitivity has occurred in workers developing photoallergy to vaporized epoxy resin.[29]

Acne and Chloracne

Lubricating oils and greases may cause comedonal plugging or a pustular folliculitis (oil acne).[30] This usually occurs on the hands and dorsal forearms, but may be particularly severe on covered areas of the body if clothing becomes saturated. Insoluble cutting oils and various other petroleum oils and greases encountered in machining operations and automotive repair work are common causes.

Chloracne is distinct from oil acne. The former may be caused by exposure to various chlorinated or halogenated naphthalenes, diphenyls, azoxybenzenes, dibenzofurans and dioxin.[31] Chloracne is characterized by a predominance of closed comedonal lesions (although some inflammatory lesions may be present), and is usually associated with the presence of noninflammatory, pathognomonic, straw-colored cysts. Involvement of the cheeks, temples, ears and postauricular areas of the face is most common, but covered areas may be involved in severe cases. Occurrences have usually been associated with massive exposures, such as industrial accidents or contamination during manufacture. The disease has its usual onset within months following initial exposure. Although acquired lesions may persist and are relatively resistant to treatment, new lesions usually cease to form within 6 to 12 months after exposure has stopped. Chloracne is a sensitive index of exposure, and is present in up to 95 percent of cases where systemic symptoms (liver disease, neurologic changes) are present.[32]

Pigmentary Disturbances

Slate gray or melanotic discoloration of the skin may result from systemic absorption of various heavy metals, such as silver, mercury or arsenic. Direct chemical staining of the skin may occur and serves as a useful marker of exposure when systemic symptoms are associated. Nitrite compounds, such as nitric acid, trinitrotoluene and dinitrophenol produce yellow stains, presumed to arise from nitration of aromatic nuclei of certain amino acids incorporated into cutaneous protein.[33] Explosive or abrasive forces may cause adventitial tattooing by embedding pigmented foreign material in the skin[34]; "coal miner's tattoo," a blue-gray discoloration from inoculation of coal dust, is an example.[35]

Nonspecific postinflammatory hyperpigmentation may follow any episode of dermatitis.[36] Photosensitizers such as tar, pitch or furocoumarins may increase pigmentation without obvious antecedent inflammation.[37] Reversibility occurs much more slowly in darkly complexioned persons than in whites. Hypopigmentation or depigmentation may also result from nonspecific postinflammatory changes, following dermatitis or thermal burns.[36]

Depigmentation resembling idiopathic vitiligo can be caused by occupational exposure to a variety of phenolic or catecholic derivatives.[38,39] These chemicals bear a structural resemblance to tyrosine and may selectively inhibit melanin synthesis; at higher doses they are cytotoxic to melanocytes. A partial list includes p-tertiary butylphenol, p-tertiary butylcatechol, p-tertiary amylphenol, hydroquinone and monobenzyl ether of hydroquinone. They serve as antioxidants or germicidal disinfectants and may be encountered with exposure to rubber, photographic developing solutions, lubricating oils, plastics or adhesive manufacture, and hospital, institutional or industrial disinfectant cleaning solutions. Depigmentation may or may not be preceded by inflammatory changes.

Urticaria

By comparison to occupational asthma, occupational urticaria is rare. Generalized urticaria, when caused by occupational exposure, usually results from inhalation of allergenic material accompanied by other symptoms of inhalant allergy. A partial list of exposures includes castor bean pomace, platinum salts, spices, penicillin, formaldehyde, aliphatic polyamines, ammonia, sulfur dioxide and lindane.[14]

Localized urticarial reactions (both immunologic and nonimmunologic) may result from exposure to a variety

of substances following percutaneous absorption. This reaction has been dubbed "contact urticaria."[15] Rarely, urticaria may become generalized. The list of substances that can provoke this reaction is constantly expanding. Some examples include flavoring and fragrances (cinnamic aldehyde), spices, antibiotics (penicillin, bacitracin), plant materials (nettles) and various proteinaceous food substances (meat, vegetables).[15] Food handlers are particularly susceptible, possibly because the skin barrier is easily damaged by water and irritating juices, facilitating percutaneous penetration.

Neoplastic Disease

The role of aromatic hydrocarbons such as coal, tar, mineral oil, lubricating oil, pitch and creosote in the induction of cutaneous papillomas, keratoses and malignant conditions has been recognized for two centuries. Percival Pott first suggested in 1775 that soot caused scrotal cancer in chimney sweeps. In 1792 tar was implicated in lip cancer. Inorganic arsenic was subsequently recognized as a carcinogen of the skin and other organs. All require a cocarcinogen for induction of neoplastic disease, of which ultraviolet light in the case of coal tar derivatives and trauma in the case of chimney sweeps are the most widely accepted.[40]

Ionizing and ultraviolet radiation may induce a radiodermatitis and neoplastic transformation, following a latency of several years.[41] Despite the large body of supporting evidence, workers' compensation boards have been reluctant to accept claims. The latent period between exposure and onset of disease, coupled with shifts in employment, complicate the issue of establishing liability to a single employer. The economic impact of accepting all skin cancer in outdoor workers as occupational disease would probably be disastrous to most insurance carriers.

The exact role of cutaneous trauma in the induction of neoplastic disease remains controversial. Skin cancer arising directly within an area of trauma has been documented on numerous occasions.[42,43] From a scientific viewpoint, evidence suggests that trauma is a cocarcinogen rather than a true carcinogen.[40]

A specific cutaneous lymphoma, mycosis fungoides, has been linked epidemiologically to work in manufacturing industries.[44] Evidence suggests that, in some cases, mycosis fungoides may evolve from chronic bouts of allergic contact dermatitis,[45] with subsequent malignant T-cell transformation.

Vascular Disease

Raynaud's phenomenon, a vasospastic disorder, may be induced in workers who use hand-held vibratory tools such as chain saws; this has been termed "traumatic vasospastic disease" or "white finger disease."[46] The responsible frequency is in the 125 Hz range, which corresponds roughly to the most sensitive frequency to which pacinian corpuscles respond.[47] Reflex linkage of chronic stimulation of the pacinian corpuscles to the sympathetic innervation of the cutaneous vasculature may be involved. The disease correlates with the duration of use of vibratory equipment, and usually does not appear until at least two years after a worker has begun to use vibratory tools.[48]

Acro-osteolysis, characterized by resorption of the distal phalanges of the hands in association with Raynaud's phenomenon, occurs in workers exposed to free vinyl chloride monomer, usually by cleaning reactors where polymerization to polyvinyl chloride is carried out.[49] Occupational scleroderma-like disorders, associated with Raynaud's phenomenon, have occurred from exposure to silica dust, expoxy resin hardener and perchloroethylene.[50] Similar disorders are alleged to be caused by a variety of pesticide exposures but the evidence is unclear.

Granulomatous Reactions

Foreign body granulomas usually present no difficulty in diagnosis. Beryllium and zirconium, when inoculated into the skin, have produced allergic granulomatous reactions; chemically induced granulomas from talc and silica have the appearance of a granuloma caused by a foreign body and do not induce hypersensitivity.[51]

Disorders of the Hair and Nails

Occupational exposure to thallium-containing rodenticides, boric acid, arsenic and chloroprene may cause a diffuse toxic alopecia[52]; hair regrowth usually starts within a few months following cessation of exposure. Ionizing radiation may similarly induce an acute toxic alopecia.

Like the skin, the hair and nails are subject to trauma and may become discolored from exposure to various dyes and other materials. Absorption of pesticides into the nail folds may result in nail plate deformation and altered growth.[53]

Disorders Caused by Infectious Agents

Poor skin hygiene may nonspecifically predispose a worker to a variety of skin infections. Abrasions and lacerations may become infected, leading to cellulitis, deep fungal infections or pyoderma. Infections associated with specific occupations include anthrax in sheep handlers and wool workers, erysipeloid in meat and fish handlers and sporotrichosis in gardeners and horticulturists. Herpetic whitlow, caused by inoculation of herpes virus into the skin of the finger, may affect nurses and dental assistants who contact oral secretions. However, a recent study, which showed that 11 of 13 cases of herpetic whitlow were caused by type II virus, suggests a venereal epidemiology for most of these infections.[54]

Disorders Caused by Physical and Mechanical Agents

Excessive heat, cold, wind, vibration and radiation (ultraviolet and ionizing) may cause a variety of direct or indirect cutaneous changes. Examples include thermal burns, frostbite, cutaneous chapping, sunburn, and acute and chronic radiodermatitis. Sweat retention under working conditions of excessive heat and humidity may result in inflammation of the sweat glands, miliaria ("prickly heat"). Vasospastic disease from vibratory tools has been discussed above.

Warm, dry air may cause generalized pruritus due to the drying effect of low humidity in the skin.[55] Large-scale outbreaks of nonspecific pruritus are not uncommon in working environments where low humidity is an important quality control measure, as in semiconductor manufacturing and electronic assembly operations.

Friction and pressure may lead to blister or callus formation on the hands of laborers. Fiberglass produces pruritus from mechanical irritation, particularly in flexural areas where the fibers may be trapped beneath clothing and rubbed against the skin. Visible cutaneous changes are usually the result of rubbing and scratching, rather than a direct effect of the fiberglass. Pruritus is directly related to fiber diameter and inversely proportional to fiber length.[56] Beta fibers are thinnest and are much less irritating.[57]

Establishing a Diagnosis

The examining physician must determine if the disease under evaluation directly resulted from occupational exposure, was unrelated or was substantially aggravated (although not primarily caused) by such exposure. The decision is based not only on medical information with which the physician is familiar but also on technical information concerning industrial processes and job performance. The physician must identify the cause as precisely as possible so that appropriate steps to avoid such exposure may be instituted and time lost from work minimized. The patient is often unable to furnish accurately all the necessary information, and telephone calls to appropriate supervisors and safety personnel, or a visit to the workplace, may be necessary. Once a list of exposures has been obtained, further identification from raw material manufacturers and technical or toxicologic information may be needed. This information may be unintentionally misleading, due to suboptimal toxicology testing procedures or inaccurate laboratory analyses. Calnan cites several such examples.[58]

During the physical examination, the physician must distinguish primarily acquired occupational skin disease from endogenous conditions (for example, atopic dermatitis or psoriasis) that may be aggravated by work, or other unrelated disorders (such as scabies). A complete examination of the entire skin surface is usually necessary. Considerable dermatologic skills and experience may be required.

The patch test is used for precise allergen identification when allergic contact dermatitis is suspected. Details of the methodology may be found in any textbook on the subject.[25] In principle, suspected allergens are occluded and are held in contact with the skin by adhesive tape for 48 hours. Localized, eczematous reactions occur within two to four days at the site of patch test application if the person is allergic to the tested substance. Because 30 percent to 40 percent of all reactions do not become positive until 72 to 96 hours after application, delayed readings are necessary.[59] Any deviations from accepted guidelines may give false positive or negative reactions.

A routine patch test screening series, available through the American Academy of Dermatology and other sources, tests only the most common, not all, allergens. Although it is extremely useful in the detection of domestic contact allergy, many allergens encountered in the workplace (gold, acrylic resins, phenol formaldehyde resins and numerous industrial biocidal agents) are not included. Unless specifically tested, these allergens may be overlooked.

Prevention

Methods to prevent occupational skin disease include protection or isolation of the worker from his environment, replacement of allergenic or irritant substances with technically suitable alternatives and removal of the worker from the work environment.[60] Removal of the worker should be considered the least desirable alternative, and should not be undertaken lightly.

Protection of the Worker

Protective clothing and barrier creams, good skin hygiene, good housekeeping and process containment through appropriate engineering controls are all means of protecting the worker. Protective clothing (gloves, boots, sleeves, aprons, coveralls and face gear) is available in a variety of fabrics; care must be taken that they work properly so that potentially noxious substances are not trapped and occluded against the skin. From a scientific viewpoint, the effect of barrier creams appears negligible.[61] However, the lubricating effects of barrier creams, when combined with a good skin hygiene program, may be beneficial.[24]

Irritant and Allergen Replacement

Contact dermatitis may sometimes be successfully managed simply by replacing the offending irritant or allergen with a suitable alternative equal to the task of the removed substance.[62,63] Substitution that is successful in eliminating dermatitis depends on precise identification of the actual irritant or allergen. Contact allergy triggered by epoxy resin may be avoided by substituting another adhesive, such as acrylic resin, when great bonding strength is unnecessary.

Future Needs

Research

Because skin disease represents 40 percent to 50 percent of all occupational illnesses, an increased emphasis on dermatologic research has been urged by the National Institute for Occupational Safety and Health[64] and others.[65] Immunological research, with emphasis on suppressor mechanisms and hyposensitization in allergic contact dermatitis, must be pursued. Mechanisms involved in causation of chloracne require further elucidation. Epidemiologic data, particularly on long-term effects of cutaneous exposures to potential carcinogens and other agents, must be developed. The sensitivity of existing toxicologic screening procedures for irritant, allergic, chloracneigenic and neoplastic potential need to be increased, and new models developed.

Education

In view of the substantial proportion of occupational illness caused by skin disease, increased participation of

dermatology as a field of study in occupational medicine curricula at the undergraduate and postgraduate levels is mandatory. Present undergraduate training in most medical centers in the United States involves relatively little training in general dermatology and virtually no training in occupational medicine. Dermatology residency programs similarly lack sufficient training in diagnosis and management of occupational skin diseases.

Cooperation of Industry

Accurate technical information and assistance is essential to the management and prevention of occupational skin disease. Industry has regarded the activities of physicians, aside from those directly employed, with great suspicion. Physicians have met resistance in the pursuit of technical information or when they have requested access to workplaces. A closer working relationship among physicians, management, and industrial safety and health personnel is essential, if future needs and goals are to be met. Complete labeling of ingredients—already a fact of life in the cosmetics industry—and material safety data sheets with accurate dermatotoxicologic information are important steps in this direction.

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Occupational Peripheral Neuropathies

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Neither clinical nor laboratory evaluation can distinguish occupational neuropathies from neuropathies due to other causes. A worker may suffer either from mechanical injury of individual nerves or from a toxic polyneuropathy that is usually axonal in type. A thorough occupational and environmental history and the recognition of clusters of cases are important in determining the diagnosis. Electrophysiologic studies are helpful in detecting neuropathies in patients who have been occupationally exposed to neurotoxins but have no symptoms. Prevention of occupational neuropathies depends on clinical vigilance, industrial hygiene surveys, biologic monitoring and periodic examination of workers exposed to neurotoxic chemicals. The development of more sophisticated methods of prevention and early detection of peripheral nerve involvement depend on understanding the mechanisms of action of toxins and the pathophysiology of the lesions they cause.

These then are the diseases that afflict men who handle lead when they work in the potter's shops. . . . Lead thought by nature chilly when pounded by that mass of stone, flares up into heat against its tormentors, sprinkles the potters with that cursed poison, carries numbness into their blood spirits, and crucifies their hands.

BERNARDINO RAMAZZINI
Diseases of Workers, 1713[1]

The risks associated with the use of lead are now well recognized, and the characteristic occupational peripheral neuropathy produced by lead is now fortunately extremely rare. Nevertheless, chronic lead exposure still represents an occupational hazard. Subtle changes in peripheral nerve function, detectable by means of electrophysiologic tests, have been found in subjects with very low levels of lead exposure.[2] The significance of these changes is debatable.[3]

Recent developments indicate that occupationally related neuropathies are still being seen by neurologists and general practitioners. New chemicals used in industrial environments may cause peripheral neuropathies to occur in clusters of exposed workers. In 1975, for example, a mysterious neurologic disorder was identified in workers at a chemical plant in Virginia[4] and traced to chlordecone (Kepone), a chlorinated insecticide. The severity of the symptoms was directly related to the dose and duration of exposure. Another example occurred in the fall of 1977, when workers at a polyurethane manufacturing plant began to have difficulty in urination.[5] The most severely affected workers had neurogenic bladders confirmed by cystometrograms and mild sensory peripheral neuropathy. A survey of the plant workers disclosed an increased incidence of urinary retention, muscle weakness, parethesias, insomnia and sexual dysfunction. Once the onset of the epidemic was recognized, a new catalyst, dimethylaminoproprionitrile, was identified as its cause.

When abused or used in a unique way, some chemicals generally regarded as harmless may cause occupational peripheral neuropathies. In 1978 three patients (two dentists and one technician) seen at the University of California, San Francisco, had sensorimotor polyneuropathy combined with signs of involvement of the posterior and lateral columns of the spinal cord.[6,7] Electrodiagnostic tests showed evidence of axonal polyneuropathy, but other laboratory tests showed no abnormalities. The only common factor in these cases was exposure to nitrous oxide. Ensuing publicity led to the recognition that a number of other patients had similar disorders. There is no proof that nitrous oxide was the

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cause of the myeloneuropathy in these patients, but indirect evidence strongly favored that conclusion.

Occupational neuropathies are often missed because the causal agent is overlooked in the formulation of the differential diagnosis. In January 1976 an outbreak of neurologic disease occurred in a chemical manufacturing plant in Texas[8] where a number of potentially injurious chemicals was used in the formation of a potent neurotoxic organophosphate, leptophos. Signs of peripheral and central nervous system toxicity were evident. Because blood cholinesterase levels were within normal limits, physicians did not initially appreciate the occupational origin of the symptoms, but attributed them to other disorders. Only retrospectively was this epidemic found to be related to exposure to leptophos and possibly to n-hexane.

Assessing peripheral nervous system function in workers may serve two purposes: to identify the chemicals that are neurotoxic to humans and to determine the level of exposure compatible with the safe handling of a potentially neurotoxic chemical.

Discovering the cause of a patient's peripheral neuropathy can be difficult. Alcoholism, diabetes mellitus, uremia and malignant disease, among other disorders, may cause peripheral neuropathy, but in approximately 25 percent to 50 percent of cases no specific cause can be found. For this reason it is important to appreciate that workplace exposure to some toxic substance may have injured the peripheral nerves. Common chemical substances that are known to be toxic to the peripheral nervous system in an occupational setting are listed in Table 1.

The purpose of this paper is to review the clinical and laboratory findings that may lead to a diagnosis of occupational peripheral neuropathy. Prevention of these neuropathies may be accomplished through the detection of workers at special risk, the monitoring of the environment, the biochemical and physiologic monitoring of exposed subjects, and the understanding of the mechanisms of toxicity.

Clinical Aspects

The clinical manifestations of peripheral nerve pathology are well recognized. Involvement of sensory fibers may lead to pain, paresthesias, hyperpathia, numbness, loss of sensation or a sensory ataxia (or combinations of these), whereas disturbed function of motor fibers may cause weakness and wasting of muscles. The tendon reflexes may be lost with damage to either afferent or efferent fibers subserving the reflex arcs. Occupational neuropathies do not differ clinically from neuropathies of other origins, but occupational history and clusters of cases may help in suggesting the underlying cause. Early detection of a single case is important not only in order that the individual patient may be shielded from further exposure to the toxic environment but also so that neuropathy may be prevented in other workers.

An occupationally related peripheral nerve lesion may result from compression or other forms of physical injury to individual nerves. Clinical findings of weakness and sensory impairment depend on the affected nerve. Severe compression or nerve transection leads to Wallerian degeneration of axon and myelin distal to the lesion, and results in wasting as well as weakness of affected muscles. Recovery is likely to be slow and is often incomplete. Mild compression leads to segmen-

TABLE 1.—*Substances Causing Occupational Peripheral Neuropathies**

Substance	*Uses/Industry*	*Reference*†
Metals		
Lead	Smelting, paint, inks, ceramics, plastics, batteries	2,3
Arsenic	Pigment production, by-product of smelting, pesticide	9
Mercury (inorganic)	Mercury cell chlorine plants, electrical apparatus, dentistry	10
Solvents		
Hexacarbons (MBK, n-hexane)	Glues, inks, shoe industry	11
Trichloroethylene	Dry cleaning, rubber production, degreasing agent	12
Carbon disulfide	Viscose-rayon production, laboratory solvent	13
Gases		
Methyl bromide	Fire extinguishers, refrigerants, fumigants, insecticides	14
Nitrous oxide	Anesthetic	6,7
Pesticides/Herbicides		
Chlordecone	Pesticide	4
Some organophosphates	Pesticides (hydraulic fluids and plastificants)	8,15
2,4-Dichlorophenoxy acetic acid	Herbicide	16
Plastics		
Acrylamide (monomer)	Waterproofing polymers, production in paper manufacture	17
Dimethylaminoproprionitrile	Catalyst in polyurethane manufacturing	5
Styrene	Production of plastics and resins	18

MBK = methyl butyl ketone.

*Environmental chemicals and drugs with neurotoxicities that are not directly related to occupational exposures have been excluded.

†The most comprehensive reference is *Experimental and Clinical Neurotoxicology* by P. Spencer and H. H. Schaumburg, (Williams & Wilkins, Baltimore) 1980. The references listed here have been chosen because they are recent, comprehensive or useful.

tal demyelination. There is no wasting of weakened muscles and recovery is rapid once the compression is relieved. Examples of such occupationally related compressive neuropathies include the anterior interosseous nerve syndrome in manual workers, ulnar nerve palsy in sedentary workers who constantly lean on the elbow, ulnar nerve lesion in the hand after recurrent mechanical trauma to the palm (for example, in operators of pneumatic drills and in those who repeatedly use shears or bang on staplers or other appliances with the palm), digital neuropathy with repeated pressure from instruments such as scissors, sciatic nerve lesions in harvesters, and peroneal nerve palsy in those who sit with crossed legs for long periods or are required to squat, as when picking strawberries.

It is more common for occupationally related hazards to lead to a polyneuropathy—that is, the symmetrical involvement of a number of peripheral nerves. Polyneuropathies may result from pathologic involvement of neurons (axonal neuropathies) or Schwann's cells (demyelinating neuropathies). Occupational toxic neuropathies are usually of axonal type and are characterized by degeneration of either the axon or the entire cell. The clinical features will differ depending on whether the predominant involvement is of sensory or motor fibers or whether there is mixed involvement of different fibers. Autonomic function is usually not affected to any great extent in occupational neuropathy; however, abdominal pain is associated with lead poisoning and bladder problems have been reported with exposure to dimethylaminoproprionitrile.

In the case of a mixed sensorimotor polyneuropathy there is usually symmetrical sensory loss, weakness and depressed or absent tendon reflexes. The clinical deficit commences distally in the extremities. It is usually more severe in the legs than in the arms, presumably because the longest axons are affected first. In some toxic neuropathies, however, motor function is affected disproportionately as, for example, in lead neuropathy or the neuropathy due to gasoline sniffing.[19] Conversely, in other conditions it is the sensory deficit that is conspicuous. Pain may be especially troublesome, for example, in the neuropathy due to arsenic. Even mild toxic polyneuropathy may predispose a patient to secondary disease of the peripheral nervous system, such as to an entrapment neuropathy. Thus, patients with a toxic polyneuropathy may, for example, present the clinical features of a carpal tunnel syndrome with little clinical evidence of more widespread pathology. Cranial nerve involvement may be conspicuous in trichlorethylene-induced neuropathy,[12] whereas a myelopathy may be a pronounced additional feature of the neurologic disorder produced by nitrous oxide[6,7] or organophosphates such as triorthocresylphosphate.[15]

Laboratory investigations can exclude other known causes of peripheral neuropathy. Nerve biopsy is rarely necessary to make the diagnosis, but it may be helpful in defining the underlying pathologic condition, especially if a connective tissue or arteritic disorder is suspected. A biopsy can also quantitate any structural changes that are present.

Electrophysiologic evaluation of a patient in whom peripheral neuropathy is suspected requires expensive equipment and the expertise of a clinical neurophysiologist, but it does have certain specific advantages:

1. It can provide objective evidence of peripheral nerve involvement and indicate the extent and severity of such involvement. This is particularly useful when clinical examination is difficult or clinical findings are relatively inconspicuous. The findings may help in distinguishing weakness or sensory symptoms due to peripheral nerve dysfunction from those due to other causes.

2. Nerve conduction studies provide quantifiable data. Comparisons are possible between groups of subjects or between data obtained from the same subject at different times.

3. Such studies can be used to identify a focal lesion of an individual peripheral nerve. This is important because many focal entrapment neuropathies may be related to occupational factors.

4. In patients with a mononeuropathy, electrophysiologic studies can indicate whether or not there is an underlying subclinical polyneuropathy that has rendered the individual nerves more susceptible to pressure or other injuries.

5. The electrophysiologic findings may indicate whether or not the predominant pathologic disturbance is axonal degeneration or segmental demyelination.

6. Nerve conduction studies are useful in epidemiologic surveys as a means of detecting heterogenicity among cases that are clinically similar. Electrophysiologic abnormalities may be detected at a time when there is no clinical evidence of peripheral neuropathy.[9]

The principles underlying nerve conduction studies are simple. If a record is made of the electric response of the muscle—that is, the compound muscle action potential—to supramaximal stimulation of its motor nerve at two points along its course, terminal motor latency and maximal motor conduction velocity along the intervening segment of the nerve may be calculated. Similarly, maximal conduction velocity and amplitude of the action potential in sensory nerves can be measured by stimulating such nerves at one point and recording from them at another. Aminoff summarizes the technical details of these methods.[20] There is, as yet, no simple and convenient method for the routine study of conduction in the most slowly conducting fibers of nerves.

Conduction velocities are reduced to a pronounced degree in the Guillain-Barré syndrome and certain hereditary or familial disorders, whereas mild slowing of conduction is found in the neuropathies associated with diabetes, uremia and certain nutritional disorders. Conduction velocity is normal or only minimally reduced when the predominant pathology is axonal degeneration rather than segmental demyelination; consequently it is usually normal in the toxic neuropathies. In such circumstances, however, the compound muscle action potential or the sensory action potential may be abnormally small because of the reduction in the number of

functional axons. If results of nerve conduction studies are completely normal, the sole electrophysiologic evidence of peripheral nerve damage may be that derived from needle electromyography. This technique will show signs of denervation in muscles supplied by affected nerves if axonal degeneration has occurred. In resting muscle, abnormal spontaneous activity, consisting of fibrillation, positive sharp waves and bizarre high frequency potentials, is found, and fasciculation potentials are occasionally encountered. During active contraction of the muscle, the number of motor units is reduced and when reinnervation of muscle fibers has occurred by collateral sprouting from surviving axons, an increased number of long duration, high amplitude and polyphasic motor units may be found.

In patients with a simple focal or entrapment neuropathy, the electrophysiologic findings are confined to the distribution of the affected nerve. There may be disproportionate slowing of nerve conduction velocity across the site of the lesion and a drop in size of the compound muscle action potential elicited by stimulating the nerve proximal to the lesion. Such findings may be superimposed on more diffuse abnormalities in those persons with clinical or subclinical polyneuropathy.

In screening patients with subclinical or minimal involvement of peripheral nerves, the most sensitive electrophysiologic means for showing any involvement will depend on the nature of the underlying disorder. Maximal motor conduction velocity is easy to determine but is often normal even in patients with clinically evident toxic neuropathy because the usual pathologic basis of the neuropathy is axonal degeneration. However, in the toxic neuropathy produced by methyl butyl ketone and some hexacarbon solvents, motor conduction velocity may be greatly reduced. Thus, in a case of n-hexane neuropathy due to glue sniffing, Korobkin and associates found delayed motor conduction velocity in the median, ulnar and peroneal nerves.[21] Nevertheless, a finding of motor conduction velocities within the normal range does not exclude the possibility of a mild neuropathy even in patients exposed to methyl butyl ketone.[22]

In neuropathy caused by exposure to acrylamide, maximal motor conduction velocity is usually within normal limits,[23] but sensory nerve action potential may be small or absent when recorded at the wrist in response to stimulation of the digital fibers of the median nerve. In cases of organophosphate neuropathy, measurement of the amplitude of sensory nerve action potential is also a very sensitive electrophysiologic screening test, although in the established neuropathy a motor deficit is conspicuous clinically while sensory findings may be minimal.[24]

Roberts[25] suggested that variation in size of the compound muscle action potential is a sensitive indicator of exposure to organophosphate compounds, but other investigators have not been able to confirm this finding.[26-28]

The prognosis for recovery from a toxic axonal neuropathy depends on the underlying cause. If exposure to the toxic substance is discontinued, further progression of the neuropathy may be halted, but any recovery is usually slow and often incomplete. Moreover, as recovery occurs in the peripheral nervous system, previously masked evidence of central involvement, such as pyramidal (corticospinal) signs, may become apparent.

Methods of Prevention

Studies in Animals

The prevention of peripheral neuropathies of occupational origin is accomplished by setting a "no adverse effect" threshold level of exposure. These thresholds are set after animal testing and are then subject to continuous revision on the basis of clinical and toxicologic observations in humans.[29] Neurotoxicology studies in animals are particularly difficult to interpret because the choice of an appropriate animal model is more critical than in other toxicity studies. Some chemicals—for example, arsenic—may cause peripheral neuropathy only in humans,[30] whereas others—such as cadmium—produce peripheral neuropathy only in animals.[31] Certain chemicals are toxic to humans and only to certain species of animals. For example, organophosphates cause peripheral neuropathy in humans and hens but not in rodents.[15] Finally, certain metals like lead cause neuropathy both in animals and humans, but its pathologic basis in experimental animals differs from that in humans.[32]

The observation of humans exposed to potential toxins is difficult. Peripheral neuropathy is a disease with an insidious onset and with clinical features that do not differentiate the cause of the disease. Underlying disease and other chemicals may also affect the pathogenesis of occupational neuropathy caused by low and prolonged exposure to toxic substances in the workplace. Animal studies of neurotoxicity are therefore necessary not only for defining any toxic effect but also for determining its mechanisms; in this way it may be possible to set no-effect levels of exposure in a more rational way.

Studies using animals provide key information about the metabolism of a chemical and about the mechanism of its action. Two examples of the successful application of findings from animals to occupational medicine are of note. Two hexacarbon solvents that have been used in many industries are n-hexane and methyl butyl ketone. In the early 1960's, outbreaks of neuropathies in Japan and Italy were related to n-hexane. Studies noted the structural similarity between n-hexane and methyl butyl ketone, suggesting the possibility of a common neurotoxic metabolite. Experimental studies in animals on the metabolism of methyl butyl ketone and n-hexane showed several intermediate metabolites with a common toxic metabolite, 2,5-hexanedione. Later, researchers using closely related compounds in which the carbonyl groups occupied different positions on the six carbon chain were unable to induce neuropathy; the neurotoxic property of 2,5-hexanedione is associated with the 1-4 spacing of the ketone groups. Because 2,5-heptanedione and 2,5-octanedione were also shown to induce the same type of experimental

neuropathy, it was suggested that the term "diketone neuropathy" be used to describe this type of neurotoxicity.[11] Similar patterns of n-hexane metabolites have been detected in the urine of workers exposed to commercial n-hexane. Thus 2-hexanol, 2,5-hexanedione, 2,5-dimethylfuran and γ-valerolactone were found as n-hexane metabolites in urine: the first two of these metabolites were positively correlated with the intensity of the exposure.[33] These results suggest that urinary excretion of hexane metabolites may be used for monitoring occupational exposure to n-hexane; the urinary level of the metabolites that is associated with a neurotoxic effect is unknown.

Two general principles emerge from these metabolism studies. First, primary prevention—that is, prevention of exposure—can be accomplished by understanding structure-activity relationships. Second, secondary prevention—prevention of toxicity by minimizing exposure—can be facilitated by the use of methods for detecting metabolites in human urine.

Another example of the relevance of animal studies to the prevention of occupational neuropathies is the case of the organophosphorus esters. Organophosphorus esters vary in their toxicity to the nervous system. The most extensively studied effect is acute toxicity, which is related to inhibition of acetylcholinesterase. However, another form of toxicity that is not related to cholinesterase inhibition is caused by some organophosphates and is called organophosphorus-induced delayed neuropathy. The primary molecular target of this form of toxicity has been identified as another esterase in nervous tissue called neurotoxic esterase. The mechanism of organophosphorus-induced delayed neuropathy is complicated, and inhibition of neurotoxic esterase is only the first step in its production.[15] These studies made possible the distinction of organophosphates with high neurotoxic potential from those with a negligible one on the basis of their affinity for neurotoxic esterase.

Organophosphates are commonly used as pesticides and their potency as anticholinesterase agents is an absolute requirement for their pesticide action, whereas an ability to phosphorylate neurotoxic esterase is not. Appreciation of the molecular targets allows accurate studies of the relationship of structure to activity and the development of organophosphates with restricted toxicity to humans.[34] Recently, in a study of this enzyme in tissues of experimental animals, neurotoxic esterase was discovered in lymphatic tissue and in circulating peripheral lymphocytes.[35] This observation suggests the possibility of monitoring exposure to neurotoxic organophosphates by measuring neurotoxic esterase in peripheral lymphocytes. Because lymphocyte neurotoxic esterase correlates with the level of inhibition in the target organ, such measurements may provide a clinical test that will reflect the interaction of a chemical with its molecular targets. Such a study was recently performed and the results indicate that the test is feasible in humans but not yet proved to be of immediate use in the setting of clinical or occupational medicine.[28]

Industrial Hygiene and Toxicology

Measurement of environmental levels of toxic chemicals and maintenance of these chemicals at safe levels are essential in preventing occupational neuropathies. Workers can also be monitored directly.

Recognition of high-risk workers. There is a debate on the emphasis that should be put on tests for identifying subjects who might be at particular risk in occupational exposures.[36] The main concern in developing such an approach is that it may lead to excluding hypersusceptible subjects from the workplace rather than attempting to clean up the environment. In general, diabetic and alcoholic workers and those with other disorders known to affect the peripheral nerves could conceivably be more susceptible to the development of a toxic peripheral neuropathy than normal workers.

Tests of exposure. These tests are based on empiric correlation between the level of certain toxins in blood or urine and the toxic effect. One of the chemicals most frequently studied is lead, the blood concentration usually being taken to indicate the severity of exposure of industrial workers. However, the blood level of a chemical does not differentiate workers with peripheral neuropathy from those without. Recently, Seppäläinen and associates[2] suggested that subclinical changes can be detected electrophysiologically in workers with blood levels of lead below 50 μg per dl, which has previously been considered a "safe" level. These results have, however, been questioned by Buchthal and Behse.[3]

Exposure tests such as the blood concentration of lead may therefore not be accurate in predicting the likelihood of developing peripheral neuropathy. They may be useful in establishing a dose-effect relationship in exposed workers when accurate and early biochemical or physiologic changes are available as an endpoint.

Tests of target response. Another series of tests are based on studies concerning interaction of the chemical with its molecular target; unfortunately, these tests of neurotoxicity are not available as they are for other target systems (for example, porphyrins for lead toxicity to the heme). If the neurotoxic esterase test for orthophosphorus-induced delayed neuropathy proves to be clinically useful, it will represent the first response test available in occupational medicine for studying peripheral neuropathies.

Methods for detection. A fourth group includes tests for early or subclinical diagnosis of the neuropathy by means of the electrophysiologic techniques described earlier.

Future advances in the comprehension of the pathophysiologic basis of peripheral neuropathies may well lead to the development of other more sophisticated measures of early detection at a subclinical level.

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New Training Opportunities in Occupational Health

Approved residency training in occupational medicine is offered at several institutions in the western states: In Northern California (a collaborative effort of the University of California School of Public Health at Berkeley and the School of Medicine at San Francisco), in Southern California (a collaboration of the University of California College of Medicine at Irvine and the UCLA School of Public Health), at Salt Lake City (University of Utah Medical Center) and at Tucson (University of Arizona Health Sciences Center). A new program is under review at the University of Washington School of Public Health and Community Medicine at Seattle. All of these are supported in part by the National Institute of Occupational Safety and Health through Educational Research Center grants.

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Hearing Conservation in Industry

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Noise-induced hearing loss is a major and entirely preventable public health problem. Effective prevention of this disorder has yet to be achieved in the United States but would improve the overall hearing health of the population more than the treatment of all other otologic disorders combined. Losses that are mild to moderately severe and maximal at 3, 4 or 6 kHz are typical but not pathognomonic. Individual differences in susceptibility are substantial but unpredictable. Hearing conservation programs are now required by the Occupational Safety and Health Administration for almost all employees whose daily exposure to noise exceeds a time-weighted average of 85 dBA (A-weighted sound pressure level). The permitted exposure level is 90 dBA time-weighted average, above which engineering or administrative controls or hearing protectors are required. Workers with lesser exposures (85 to 90 dBA time-weighted average) who have hearing changes must be similarly protected. Many, but not all, elements of required hearing conservation programs have been specified recently by the Occupational Safety and Health Administration. Medical supervision and otologic referral are important components of hearing conservation programs because otologic problems other than noise-induced hearing loss are common in industrial populations. Compensation for noise-induced hearing loss, which is awarded through state workers' compensation boards, as well as certain federal sources, varies widely.

The association between prolonged exposure to intense sound and hearing loss was apparently recognized by Pliny the Elder, who described deafness among people living near the cataracts of the Nile River.[1] However, there are very few sounds in nature loud enough to cause hearing loss, and noise-induced hearing loss (NIHL) did not emerge as a significant problem until the industrial age. Even then NIHL tended to be eclipsed by more serious industrially related health problems, such as accidental injury and pulmonary disease. In the United States, redress for occupational injury or illness, and much of the impetus for preventive measures, came from the development of workers' compensation boards at the state level. Hearing loss has been recognized as a compensable occupationally related illness by a majority of the states only since 1965, and there are still some states that do not recognize NIHL as a compensable condition. This is partly because a somewhat artificial distinction was made in the past between injury and illness; in some cases, a gradually developing condition, such as NIHL, had to be considered as an accretion of minute injuries in order to be covered. There is still considerable variation among the state compensation laws; in addition, the federal government has separate standards within the Veterans Administration and the Department of Labor covering compensation of different beneficiary classes. A recent survey of these laws has been provided by Fox.[2] Table 1 gives some idea of the wide range of compensation benefits available.

While the threat of compensation payment provided some incentive for employers to reduce noise exposures, the variability among states and the fear by many employers that beginning a hearing conservation program would actually increase the number of claims, made this incentive rather weak. By 1970 most workers ex-

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ABBREVIATIONS USED IN TEXT

NIHL = noise-induced hearing loss
OSHA = Occupational Safety and Health Administration
TWA = time-weighted average

posed to hazardous noise levels were still not covered by hearing conservation programs.

The modern history of hearing conservation in the United States began in 1969 with the promulgation of a noise standard under the authority of the Walsh-Healy Act. This act required hearing conservation programs for industries engaged in federal contract work if their employees were exposed to a daily equivalent of eight hours at 90 dBA.* The Occupational Safety and Health Act, passed in 1970, extended the requirement for hearing conservation programs to industry at large in the United States.[4] The Occupational Safety and Health Administration (OSHA) within the Department of Labor was charged with formulating specific regulations for hearing conservation programs, a task which at this writing is still incomplete. A proposed text for a definitive Hearing Conservation Amendment was published by OSHA in January 1981,[5] but was almost immediately stayed by President Reagan's executive order creating a moratorium on expensive new federal regulations. An abbreviated version of the Hearing Conservation Amendment was printed in the *Federal Register* in August 1981 and now has force of law.[6] Many other provisions of the amendment are still under review by OSHA, and a final version of the complete Hearing Conservation Amendment will probably be published in late 1982.

Despite the incomplete nature of the OSHA Hearing Conservation Amendment, hearing conservation programs are now required by law for all employers engaged in interstate commerce whose employees have hazardous noise exposures. This definition is quite liberally interpreted, and very few businesses are considered by OSHA *not* to be involved in interstate commerce. The regulations currently in force will be discussed later in this paper.

Noise-Induced Hearing Loss

NIHL is, after presbycusis, the most common form of hearing loss in the United States, probably affecting about five million Americans (precise estimates are not available). NIHL results from *chronic* acoustic overstimulation of the ear, and is generally distinguished from acoustic trauma, an injury resulting from sudden air pressure changes of such magnitude that gross mechanical damage is done to both the middle and inner ears. (This requires a peak overpressure around 150 dB.)

Pathologically, NIHL is associated with damage to, and ultimately loss of, hair cells in the organ of Corti. The outer hair cells, especially in the basal turn, are the most susceptible. Afferent neuron loss is minimal and predictable based on secondary degeneration from inner hair cell and supporting cell loss.

*dBA is a measure of the A-weighted sound pressure level. The A scale on a sound level meter deemphasizes the low frequency sounds that are less likely to be harmful to hearing.

TABLE 1.—*Compensation for Noise-Induced Hearing Loss*

Jurisdiction	*Maximum Compensation*		*Compensation for "Typical" Loss**
	One Ear	*Two Ears*	
Massachusetts	$ 4,500	$ 12,000	$ 0†
North Dakota	2,000	8,000	810
California	3,157	21,770	2,204
Washington	14,400	28,800	2,916
District of Columbia	23,724	91,248	14,600
US Dept of Labor	37,585	144,556	23,129
Veterans Administration	17,400‡	181,200‡	0§

*Pure-tone thresholds: 20 dB at 0.5 kHz, 22 dB at 1 kHz, 34 dB at 2 kHz, and 51 dB at 3 kHz. This is the *mean* audiogram of workers applying for compensation to the US Office of Workman's Compensation Payments, as reported in Hardick, et al.[3]

†Must be total loss to be compensable.

‡Monthly compensation payments of $58 and $604, respectively, with annual cost-of-living increases, for 25 years.

§VA stipends, although generous for more severe losses, are not payable for losses as mild as the one used in this example.

Audiologic Features

The classic audiogram of early or moderately advanced NIHL shows normal hearing in the low frequencies and a gradually increasing loss with a maximum at 3, 4 or 6 kHz and some return of function at 8 kHz. The audiometric shape cannot be considered pathognomonic, since many other otologic disorders can produce hearing losses of the same pattern and NIHL may not show the typical return at 8 kHz in some cases. When the audiogram is *consistent* with NIHL (as in most patients with sensorineural hearing losses), it is impossible to determine the cause from a single set of audiologic data alone; even the most sophisticated audiologic tests will not separate NIHL from other disorders which cause cochlear damage (for example, aminoglycoside ototoxicity, head injury, presbycusis). A careful and detailed medical history, ideally supported by frequent audiometric measurements (before, during and after any potentially hazardous exposure or event) and estimates of the severity of the hazard in question (sound level measurements, antibiotic serum levels, associated injuries) is the only basis for a confident etiologic diagnosis.

A worker exposed at constant level and duration throughout his career may show progressive loss in the 3 to 6 kHz region up to about 15 years after the beginning of that exposure, after which the loss in the high frequencies begins to plateau. Hearing loss at 1 and 2 kHz has a more gradual onset and may progress over a period of up to 40 years, so that, in the latter part of the worker's employment, the loss appears to stabilize in the high frequencies and to "invade" the low frequencies. Thus, it can rarely be said, except for workers with severe hearing losses, that further exposure to the same noise levels and durations will not cause further damage. Figure 1 shows the differing time course of hearing loss for the low and high frequencies.

It is notable that in large populations of noise-exposed workers, after exclusion of obvious non-noise-

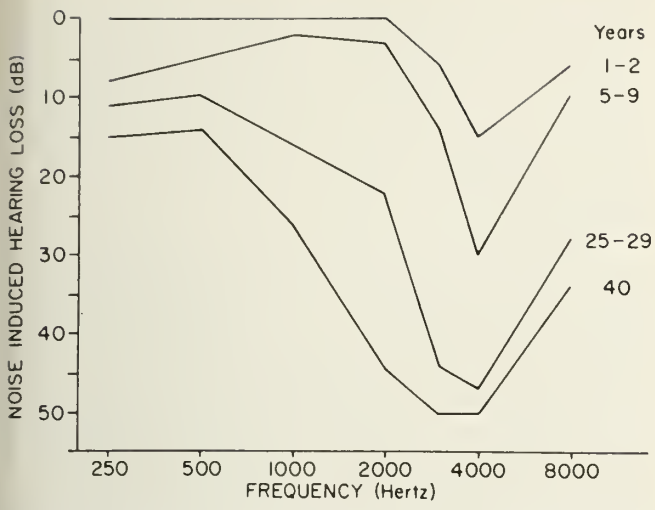

Figure 1.—Audiometric patterns seen after increasing durations of exposure to a very loud (more than 100 dBA) industrial environment. The parameter is the number of years of exposure. (Reprinted with permission from Melnick.[7])

induced otologic disease, thresholds rarely exceed 75 to 80 dB. Since NIHL, as distinguished from acoustic trauma of an explosive nature, does not cause profound hearing loss or deafness, other causes, such as superimposed presbycusis, hereditary degenerative losses or ototoxic damage, must be sought in such cases. Audiograms are usually symmetrical, although modest degrees of asymmetry may be present,[8] especially when there is a clear history of asymmetry of exposure, as in the case of hearing loss from rifle or shotgun use. A right-handed hunter will tend to expose his left ear directly to the muzzle noise while the right ear is shielded by the head shadow, particularly from the effects of the high frequency components of the noise. However, most factory environments are so highly reverberant that shadow effects protecting one ear are unusual. Asymmetries exceeding 40 dB at any two adjacent standard audiometric frequencies are unlikely to be caused by occupational noise exposure.[9]

What has been described so far as NIHL is the stable hearing loss present after the individual has been away from loud noise for many hours (preferably, days). It is extremely important to distinguish (at least in principle, if not quantitatively) between a person's total hearing loss and the *portion* of that loss attributable to occupational noise. Presbycusis, socioacusis (usually understood to mean hearing loss from exposure to nonoccupational noise) and nosoacusis (hearing loss due to other otologic disease) are present in every industrial population and account for a substantial portion of the hearing loss seen in workers. For large groups, but not for individuals, these factors can be accounted for by comparing noise-exposed with appropriately matched non-noise-exposed workers. The amount of hearing loss attributable to occupational noise is often called noise-induced permanent threshold shift. Parenthetically, much of what passes for presbycusis is probably really "socioacusis" due to the nearly ubiquitous noise pollution of modern society; there are scanty data to indicate that aged persons in nonindustrial societies have much better hearing than even "non-noise-exposed" older Americans. Noise-induced permanent threshold shift must also be distinguished from the temporary threshold shift that is present immediately after exposure to loud noise. Unlike a permanent shift, in the latter case hearing gradually returns to normal. In general, noises that over a lifetime will cause substantial permanent threshold shifts will also cause a temporary threshold shift on a single exposure. However, this relationship is not absolute, and cannot be used as a way of defining permissible noise exposures. Temporary threshold shift is an important factor in audiometric testing programs because an audiogram taken at the end of a worker's shift may considerably overestimate his true hearing loss. A period of 14 hours of "effective quiet" (levels less than 80 dBA) before testing is generally enough to allow a valid measure of hearing levels.

It is believed that NIHL does not progress after the cessation of noise exposure. Although there is no way of proving in an individual case that progressive hearing loss is *not* somehow due to prior noise exposure, experts who have reviewed many thousands of industrial audiograms state that workers whose hazardous exposures have ceased have no more subsequent hearing loss than would be expected from the normal aging process (W. Dixon Ward, PhD, professor of otolaryngology, University of Minnesota, and Aram Glorig, MD, of the Otologic Medical Group, Los Angeles, written communications).

Hearing Handicap

The communication handicap imposed by NIHL, as is true for any sensorineural hearing loss, is hard to determine precisely, but must be estimated for compensation purposes. For the sake of simplicity, it is generally agreed that handicap should be defined in terms of impairment in the most basic and important of hearing functions, the perception of speech. The ability of a person to understand speech will depend on more than just pure-tone thresholds. Age, intelligence, ability to supply missing cues from the context of redundant messages and the difficulty of the person's usual auditory environment are all important factors. In addition, the cochlear pathology itself may vary in such a way that two persons have identical pure-tone thresholds, but one suffers a much greater distortion of hearing, thus reducing speech intelligibility. Speech discrimination scores would seem to be valuable in this context, but are of limited usefulness because there is as yet no widely accepted test of speech discrimination that is both well standardized and a realistic simulation of "real world" listening situations. For these reasons, hearing handicap is usually estimated from pure-tone audiometric thresholds. (An exception is the system used by the Veterans Administration for rating service-connected disability.) The most widely used formula, which has been accepted (sometimes with modifications) by a majority of the states, is that proposed by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology—Head and Neck

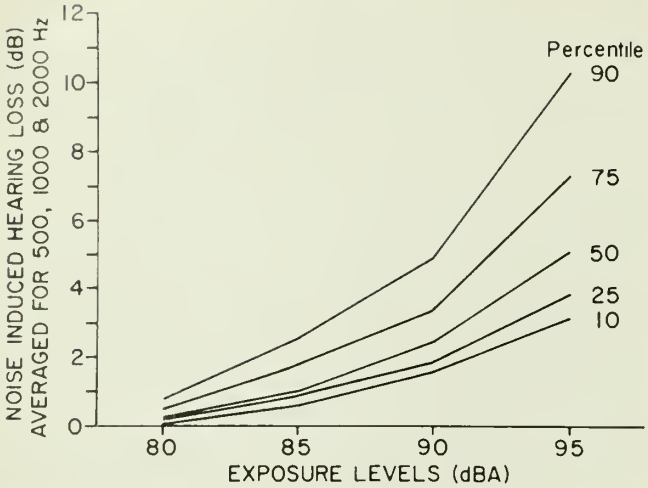

Figure 2.—Relation of hearing loss, after correction for presbycusis, at 0.5, 1 and 2 kHz, to intensity of exposure over 40 years. The parameter is percentile, and shows the effects of individual variation in susceptibility. The threshold shifts shown do not represent the more severe effects on higher frequencies. (Reprinted with permission from Melnick.[7])

Surgery in 1979, and adopted by the American Medical Association the same year.[10] Almost half of the states leave the choice of formula to the discretion of the physician. The American Academy of Otolaryngology-American Medical Association formula for hearing handicap makes several assumptions, all recognized to be necessary oversimplifications:

1. The frequencies most important for understanding speech are 0.5, 1, 2 and 3 kHz.

2. Material impairment of hearing begins when the pure-tone average exceeds 25 dB (this is not the same as the line between "normal" and "abnormal" hearing; for children and young adults, thresholds greater than 15 dB may be considered abnormally elevated).

3. Impairment grows at the rate of 1.5 percent per dB of average hearing loss beyond the 25-dB "fence" until a 100 percent impairment is reached at 91.7 dB.

4. A total unilateral hearing loss is much less handicapping than bilateral moderately severe losses. Thus, equal weighting of hearing losses in the two ears is unreasonable. Empirically, a five to one weighting, favoring the better ear, is chosen.

Pure-tone averages are calculated for each ear by summing thresholds at 0.5, 1, 2 and 3 kHz and dividing by 4. Next, 25 dB is subtracted from each pure-tone average, and the resulting figures are multiplied by 1.5. These individual ear impairment scores are then combined into the hearing handicap score by multiplying the score for the better ear by 5, adding to it the score for the worse ear and dividing by 6. The final handicap score is a number between 0 and 100 percent. A typical applicant for compensation for NIHL will have, by this formula, about a 10 percent hearing handicap (see Table 1). Scores over 50 percent are unusual. It is then up to the state or other agency using this figure to determine disability and appropriate compensation. There is, of course, no treatment for NIHL. Hearing aids help to a highly variable degree, as does aural rehabilitative training, which includes lip-reading and other communicative strategies. However, the amelioration of handicap offered by these rehabilitative efforts is not usually considered by the states in awarding compensation.

Susceptibility

As is clear from Figure 2, major individual differences in susceptibility to NIHL exist. Unfortunately, there is no good way, as yet, to identify the "tender" and "tough" ears in advance, which would allow the exclusion of more susceptible workers from hazardous areas. The effects of age and prior hearing loss appear to be equivocal. Men seem to be more susceptible to NIHL than women, but it has been suggested that this difference is confounded by differences in work schedules, in nonoccupational exposures (for example, hunting) and compliance with hearing conservation regulations. Smoking and relative lack of pigment (as expressed by eye and skin color) have been suggested as possible risk factors for NIHL, mostly on the basis of studies of temporary threshold shift, but are not accepted as criteria on which to base hearing conservation decisions. An obvious candidate for a predictor of susceptibility to NIHL would be an individual's susceptibility to temporary threshold shift. However, this has not been shown to correlate well with subsequent NIHL. At any rate, variability in susceptibility to NIHL is not great enough to suggest that the problem could be solved by simply excluding a few workers with tender ears from the factory. Thus, the thrust of industrial hearing conservation programs has been to reduce exposure for all workers.

Extraauditory Effects of Noise

Loud noise can have many deleterious effects, in addition to damaging hearing. Interference with speech communication can be fairly well predicted by sound level measurements. An equally well-known, but much less predictable, effect of noise is annoyance. Subjective factors must be considered; for example, people consider noise they make themselves less annoying than noise others make. Intermittency, which is a protective factor for NIHL, increases annoyance. Time of day is also important: 10 dB are usually added to the levels of noises made between 11:00 PM and 7:00 AM by community noise experts attempting to predict annoyance caused by different noises.

Whether noises can cause serious physiological changes other than hearing loss is still controversial. In both animals and humans, short-term noise exposures, usually in contexts that are otherwise stressful, cause increased plasma catecholamine and corticosteroid levels and increased pulse and blood pressure levels.[11] Some poorly controlled clinical data suggest a relationship between prolonged noise exposure and hypertension. However, it is probably still safe to say that no serious adverse health effects have been documented for noise exposures that do not exceed the permitted ex-

posure level set by the Hearing Conservation Amendment discussed later in this paper.

Damage Risk Criteria

Intensity

Three factors determine whether a noise exposure is hazardous. Most obvious is the intensity of the sound. This must be measured at a point representative of the ear of the listener rather than at the source because the intensity of sound decreases by 6 dB for every doubling of the distance from the source. (This is strictly true only in an open field, and cannot be relied on in a typically reverberant industrial environment.) It is important to remember that the decibel scale is logarithmic; every 10-dB increase represents a tenfold increase in sound energy. Thus, if one of two identical sound sources (for example, two assembly lines) is shut down, the total noise level will be reduced by only 3 dB, a halving of the sound energy.

Spectrum

The second important factor is the sound spectrum. In general, a noise with mostly high frequency components, such as a jet engine's whine, will be more damaging than a noise of equal intensity that is dominated by low frequency components. Most sound level meters contain a weighting network that takes this factor into consideration. So-called A-scale readings accentuate sound levels in the high frequencies to which the ear is most sensitive, and greatly attenuate sound levels above and below these frequencies. Table 2 shows the relationship of various everyday sounds to dBA readings, at the ear of the operator if not otherwise specified.

The level at which, over a lifetime of exposure, there is some risk to hearing is still a matter of controversy. Figure 2 illustrates some well-accepted data, showing that levels up to 80 dBA cause negligible changes in average thresholds at 0.5, 1 and 2 kHz.

Forty years of exposure to levels up to 90 dBA cause a median noise-induced permanent threshold shift, after correction for presbycusis, in the high frequencies (3, 4 and 6 kHz) of less than 15 dB; for lower frequencies, the loss attributable to noise is well under 10 dB.[5] While more susceptible ears will suffer greater loss (about a 20-dB high-frequency noise-induced permanent threshold loss for a worker at the 10th percentile), these shifts are not in themselves handicapping. However, when these shifts are added to the normal changes caused by aging, about 20 percent of workers, in *excess* of those who would cross the arbitrary 25-dB impairment "fence" in the absence of noise exposure, will be found to have significant hearing impairment after 40 years of exposure to 90 dBA for eight hours a day. Thus, a 90-dBA permitted exposure level cannot be considered adequate to protect all workers from handicapping hearing losses. Current OSHA regulations impose a 90-dBA standard and depend upon audiometric monitoring to detect persons with "tender" ears and exclude or protect them from further exposure.

TABLE 2.—*Typical Noise Levels*

Noise Source	*dBA*
Oxygen torch	120
Compactor	115
Chain saw	110
Snowmobile	105
Jet flyover (1,000 feet overhead)	100
Power lawnmower	95
Motorcycle (25 feet)	90
Milling machine, diesel truck (50 feet away)	85
Garbage disposal, lathe	80
Dishwasher	75
Television	70
Conversation	65
Air conditioning (20 feet away)	60

TABLE 3.—*Permissible Daily Exposures**

Level (dB)	*Duration (hours)*	*Time-weighted Average (dBA)*
85	16	90
90	8	90
95	4	90
100	2	90
105	1	90
110	1/2	90
115	1/4	90
120	1/8	90
125	1/16	90
130	1/32	90

*OHAS.[6]

Time

The third important factor is time. Even noises above 110 dBA cannot be labeled as hazardous per se. Rather, it is the noise *exposure* that is hazardous, and this must take into account the duration of exposure. Eight hours a day at a given level is more hazardous than four, which is, in turn, more hazardous than two hours a day. The exact trading relationship between time and intensity is controversial. If one wanted to equate sound energy, a 3-dB doubling rule would be appropriate; thus, 85 dBA for eight hours delivers as much sound energy to the ear as 88 dBA for four hours. However, this relationship is complicated by another temporal factor: intermittency. Even the shortest interruption of sound exposure allows the ear to recover somewhat, with a lesser degree of permanent hearing loss than would occur if the exposure were delivered continuously. This factor is difficult to incorporate into exposure calculations in a practical way, but it is known that very high-level industrial exposures tend to be more frequently interrupted than more moderate noise levels. In addition, the epidemiologic data and information on temporary threshold shift do not support a simple 3-dB doubling rule, suggesting that there may be nonlinearities in the ear's response to increasing levels of noise. For these reasons, OSHA has adopted a 5-dB doubling rule.

Time-Weighted Average

The factors of intensity, spectrum and time are all combined in a single measurement that estimates the

hazard of a particular exposure: the time-weighted average (TWA), the level of sound measured on the A scale and converted to an eight-hour basis. Thus, a 90-dBA continuous noise for a period of eight hours would yield a TWA of 90 dBA. An exposure to the same level for only four hours, however, yields 85 dBA TWA; if only for two hours, the exposure would be 80 dBA TWA, because of the 5-dB doubling rule. Modern noise dosimeters can calculate the TWA by integrating a worker's exposure throughout the day to noises of different intensity levels, even including impulse noise up to 130 dB. However, very brief and very intense sound impulses have damaging effects that are difficult to predict from a simple time-weighted average of this sort.

Management of a Hearing Conservation Program

Permitted Exposure Level

At the time of this writing, the permitted exposure level is 90 dBA TWA.[6] Exposures of less than eight hours to higher levels of noise are permissible (see Table 3), but exposures at more than one level must be added together. For example, one hour at 100 dBA plus one quarter of an hour at 110 dB equals 90 dBA TWA, although either alone would equal 85 dBA TWA. Exposures above the permitted exposure level must be reduced by engineering means, by administrative action (such as reducing the time of exposure of an employee) or by the use of hearing protectors when the first two measures are infeasible.

Although the permitted exposure level is 90 dBA TWA, hearing conservation programs must be instituted by employers whose workers have exposures exceeding 85 dBA TWA.[6] Employers are responsible for determining whether they must institute a hearing conservation program. In general, any workplace noise that is loud enough to interfere with speech communication or to cause employee complaints of tinnitus or temporary hearing loss may be hazardous. In such cases, sound level measurements should be made.

Components of a Hearing Conservation Program

Required components of a hearing conservation program include exposure monitoring, employee notification and training, a program of periodic audiometry, the provision of hearing protectors to all workers exposed above the permitted exposure level (and to workers whose exposures are in the 85 to 90 dBA "gray zone" and who are found to have worsening hearing over time), and appropriate program supervision, review and record keeping.

At present, area monitoring of noise levels as well as personal noise dosimetry for individual workers is permitted. Monitoring must be repeated whenever changes in equipment or procedures that may increase noise exposures occur.

Audiometry

Baseline and annual periodic audiograms must include 0.5, 1, 2, 3, 4 and 6 kHz. Significant threshold shifts must be noted and appropriate action must be taken. Unfortunately, the significant threshold shift is one of the factors that OSHA has not yet defined, although field enforcement officers are instructed to consider a 20-dB shift at any frequency to be a significant threshold shift. Many experienced program managers and consultants believe that the use of pure-tone averages—for example, a high-tone average at 3, 4 and 6 kHz and a low-tone average at 0.5, 1 and 2 kHz—reduces test/retest variability, and that a 10-dB shift in either of these pure-tone averages is more significant than a 20-dB change in a single frequency. OSHA is expected to decide on this point soon. Appropriate action, when a significant threshold shift occurs, includes employee notification, the fitting of hearing protectors to workers (exposed to 85 to 90 dBA) who had not previously been required to use them and the refitting and retraining of employees who *had* previously been required to wear them. If the employer has reason to believe that the plant audiometry is invalid, or that the patient is suffering from a medical problem, he is required to refer the worker to an audiologist or to a physician. However, there is no *systematic* requirement for outside referral.

Supervision

Hearing conservation programs must be supervised by a professional—either a physician or audiologist. Such supervision may, however, be on a contractual, occasional basis. Specifically, specially trained industrial audiometric technicians (many of whom are plant nurses) may actually carry out the audiometry and keep the records, and the scoring of audiograms and comparison of one year's audiogram to previous audiograms may be done by these persons or by computer programs, providing that such programs have been set up with the appropriate professional input. Ultimately, the prevention and management of hearing loss is a medical responsibility, and direct medical supervision of hearing conservation programs is highly desirable.

Otologic Referral

One important area in which OSHA has been silent is otologic referral. The main goal of a hearing conservation program is to prevent NIHL, but an important secondary goal is the detection of hearing loss caused by other disorders, and the appropriate management of hearing loss from all causes. Obviously, it is not necessary to refer all workers who have threshold shifts for otologic evaluation, but certain generalizations can be made about the characteristics of those hearing losses most likely to be due to disorders other than NIHL:

1. NIHL is usually symmetrical whereas other otologic disorders, especially the more serious and treatable ones, are often asymmetrical.

2. NIHL usually progresses slowly; other otologic disorders often progress rapidly.

3. Any hearing loss, whether due to NIHL or other causes, which reaches a ratable hearing handicap (that is, a pure-tone average in excess of 25 dB in either or both ears) is likely to be substantially handicapping to

TABLE 4.—*Criteria for Otologic Referral**

Baseline

1. Average hearing level greater than 25 dB at 0.5, 1, 2 and 3 kHz in either ear
2. Difference in average hearing level between the better and poorer hearing ear of:
   - more than 15 dB at 0.5, 1 and 2 kHz or
   - more than 30 dB at 3, 4 and 6 kHz

Periodic

3. Change, in any frequency in either ear, from baseline:
   - more than 15 dB for the average of 0.5, 1 and 2 kHz or
   - more than 20 dB at 3 kHz or
   - more than 30 dB at 4 or 6 kHz

Miscellaneous

4. Variable or inconsistent audiometric responses, otologic signs or symptoms (for example, otorrhea)

*Recommended by The American Academy of Otolaryngology—Head and Neck Surgery.

the individual, who may benefit from hearing aid use, even if medical and surgical management are not feasible.

Criteria based on these generalizations were used to select workers for otologic referral in a recent study.[9] Half of the referred workers had otologic disorders other than NIHL, or required medical or rehabilitative management.

Criteria for otologic evaluation must be distinguished from definitions for a significant threshold shift. A significant threshold shift should be defined in such a way as to detect the smallest genuinely measurable change in hearing, so that a worker's exposure may be reduced and further hearing loss prevented. Criteria for otologic referral, on the other hand, are intended to select those workers with substantial audiometric abnormalities who are most likely to have otologic disorders other than NIHL or to require rehabilitation. A significant threshold shift generates in-plant action, such as fitting of hearing protectors and counselling, while otologic referral is required for a smaller proportion of workers with more substantial threshold shifts.

In the study referred to above,[9] the highest yield from otologic referral was in those workers who were referred on the basis of their *baseline* audiograms, either because of substantial hearing handicap or because of asymmetry. OSHA does not require any action to be taken because of baseline abnormalities. Yet this is not in the best interest of employees, who frequently have untreated otologic problems. It also benefits employers to refer workers with baseline abnormalities. Quite apart from any good will accrued by the employer, he will benefit from knowing the precise hearing status of the employee at the time he begins his employment, in case of later compensation claims. Plant audiometry is less precise and reliable than clinical audiometry, and is particularly vulnerable to error in cases where moderate or severe hearing loss already exists, or where there is significant asymmetry between ears. The American Academy of Otolaryngology—Head and Neck Surgery has recommended a set of criteria for otologic referral,[10] which are reproduced in an abbreviated form in Table 4.

Conclusion

Noise-induced hearing loss is a relatively new public health problem, affecting mostly industrial societies. Effective prevention of noise-induced hearing loss is still an unrealized goal for the United States as a whole, although the principles of how to effectively manage an industrial hearing conservation program are fairly well known.

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Effects on the Liver of Chemicals Encountered in the Workplace

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The liver plays a central role in toxicology. It is the primary organ of detoxification and elimination by metabolism of many chemicals. Many workplace chemicals can affect the liver in animals; fewer have been proved to do so in humans. The diverse hepatic effects observed in humans from occupational exposure to chemicals range from fatty infiltration, acute hepatitis and cholestasis to cirrhosis and angiosarcoma. Three important workplace chemicals, prototypes for the toxicities of many others, are carbon tetrachloride, vinyl chloride and the polychlorinated biphenyls (PCB's). These three are described in some detail to highlight principles of occupational toxicology. Most of the hepatic effects produced by chemicals in the workplace have clinical, laboratory and morphological features common to many other forms of liver disease. Therefore, only an astute physician who takes an occupational history will recognize the association between a patient's workplace and liver disease.

The path to diagnosis of hepatic injury produced by a chemical in the workplace is not straight. Apart from instances when a chemical produces a specific lesion, hepatic injuries produced by chemicals do not have unique clinical, laboratory or morphologic features. Toxic hepatitis, cirrhosis, portal hypertension and hepatocellular carcinoma are found with such frequency in the general population that an association between these lesions and an occupational chemical is either not recognized or difficult to prove. Clinical manifestations of acute or chronic liver diseases are often not specific enough to allow diagnosis of the cause. Furthermore, the laboratory examinations that we carry out to test liver "function" are not specific and are usually not sensitive. One laboratory test, serum γ-glutamyl transpeptidase (GGTP) activity, is more sensitive to acute hepatic damage than other serum enzyme studies. However, GGTP activity increases in the presence of many other diseases and also after consumption of drugs and alcohol, so this index must be interpreted carefully. Histologic examination of biopsy specimens may be useful to test other organs or tissues, but liver biopsy, because it is invasive, is done rarely in asymptomatic or mildly symptomatic workers. In addition, most histologic features are commonly caused by many toxins. Epidemiologic studies that can associate workplace chemicals with hepatic changes not only require large cohorts of workers but also are difficult to carry out—particularly prospective studies. Epidemiologists must match the exposed population to the control population for factors such as alcohol and drug intake, previous liver disease and life-style. All of these factors could produce hepatic injury not related to the chemical or enhance the hepatic effects of the chemical being studied.

That an individual patient's liver disease is related to the workplace will only be recognized by a physician who understands the significance of the patient's job. The medical history of any patient with liver disease should include a complete history of previous and current occupations and potential exposure to chemicals. In this review I will discuss some concepts fundamental to the understanding of the effects of chemicals on the liver.

The liver plays a central role in toxicology. Lipophilic chemicals that the body encounters are usually elimi-

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ABBREVIATIONS USED IN TEXT

CCl_4=carbon tetrachloride
GGTP=γ-glutamyl transpeptidase
NIOSH=National Institute for Occupational Safety and Health
OSHA=Occupational Safety and Health Administration
PCB=polychlorinated biphenyl

nated at least in part by the liver through one or more metabolic steps. Metabolism usually detoxifies a potential toxin but can "activate" many important chemicals by metabolizing them to active forms, often more toxic than the parent chemical. The liver is the first organ after the gastrointestinal tract that is exposed to an ingested chemical. Therefore, concentrations in blood entering the liver are higher than those encountered by any other organ. Consequently, the liver's potential for injury by the chemical is greater.

The liver shows a marvelous diversity in the chemicals it can eliminate, which range from elements such as phosphorus and arsenic to polyhalogenated complex molecules such as the pesticide chlordecone or such widespread environmental contaminants as polyhalogenated biphenyls. As will become evident in this review, the "responses" of the liver to exposure to these chemicals are also numerous, diverse and as fascinating as normal liver "function."[1] The hepatic responses range from fatty infiltration to cell death and necrosis, from metabolic changes such as proliferation of the smooth endoplasmic reticulum to porphyrias, from infiltration by granulomas to cirrhosis, from the vascular lesion of peliosis hepatitis to angiosarcoma and from parenchymal cell adaptation to neoplasia. One chemical may produce more than one response in the liver with the type of response often determined by factors such as dose, age, route of exposure, exposure to other chemicals or drugs, presence or absence of liver disease and inherent sensitivity of the exposed person to the chemical.

Thousands of the chemicals currently in use in the workplace can produce hepatic injury in animals. Fewer have produced hepatic injury in humans. Some occupational chemicals that can affect the liver are listed in Table 1.[2] The list includes some compounds that have only been evaluated in animals. The number of occupations involved even in the use of one chemical can be large. For example, allyl alcohol is used by manufacturers of acrolein, allyl ester, drugs, fungicides, glycerine, herbicides, organic chemicals, plasticizers and resins. Xylene is used in many capacities in the occupations listed in Table 2. However, workers in these occupations not only use xylene but also a variety of other chemicals that are potentially hepatotoxic or can interact with each other to produce hepatic injury. Listed in Table 3 are the more important workplace chemicals that have affected the liver in humans, some occupations in which they are used and the hepatic responses to them. In this review the hepatic effects in humans of three chemicals that can be regarded as prototypes of a number of other compounds and illustrate many of the concepts fundamental to understanding the effects of chemicals on the liver will be examined.

TABLE 1.—*A List of Workplace Chemicals That Have Produced Hepatic Effects in Animals or Humans, or Both*[2]

2-Acetylaminofluorene	Ethyl silicate
Allyl alcohol	Fluoroalkenes
Antimony	Gasoline
Arsenic	Germanium tetrachloride
Arsine	Hydrazine
Benzyl chloride	Iron pentacarbonyl
Beryllium	Mercaptans
Bipyridyl	Metal carbonyls
Boron hydride	Methyl chloride
Cadmium	4,4-Methylenebis (2-chloroaniline)
Carbon disulfide	Nickel
Carbon tetrachloride	Nitrobenzene
Chlorinated benzenes	Nitroparaffins
Chlorinated naphthalenes	n-Nitrosodimethylamine
Chlorodiphenyls	Phenol
Chloroform	Phosphine
Chromium	Phosphorus
Cresol	β-Propiolactone
1,2-Dibromoethane	Propylene dichloride
1,2-Dichloroethane	Pyridine
Dimethyl acetamide	Selenium
4-Dimethylaminoazobenzene	Tetrachloroethane
Dimethylformamide	Tetrachloroethylene
Dinitrobenzene	Tetryl
Dinitrophenol	Thallium sulfate
Dioxane	1,1,2-Trichloroethane
Diphenyl	Trichloroethylene
Epichlorohydrin	Uranium
Ethanolamine	Vinyl chloride
Ethylenediamine	Xylene
Ethylene glycol ethers	
Ethyleneimine	

Carbon Tetrachloride

Carbon tetrachloride (CCl_4) is used either in a chemically pure grade or a technical grade (which contains other chlorinated hydrocarbon impurities). It is a colorless liquid that is volatile (vapor pressure is 91.3 mm at 20°C) and decomposes to the irritant gas phosgene in the presence of small amounts of water and heat (greater than 250°C). A quantity of 1 ppm is equivalent to 6.3 mg per cu meter. Carbon tetrachloride was synthesized first in 1839. Several reviews of its use and toxicity are available.[3-6] It was introduced as an anesthetic agent in 1847, an analgesic in 1867, a shampoo in 1909 and anthelmintic drug in 1921. Industrial production began on a large scale in the United States in about 1907, and production of this chemical was about 4.5 million kg annually in 1914, reaching 390 million kg by 1976. The compound is used primarily for synthesis of fluorocarbons but it is also a solvent, degreaser, raw material for organic chemical synthesis and a fire extinguisher. Carbon tetrachloride, used as a spot remover in the fabric care industry and at home, was banned in the United States on November 11, 1970, by the Food and Drug Administration. In the United States the Occupational Safety and Health Administration's (OSHA) standards require that an employee's exposure to CCl_4 at no time exceed a time-weighted average of 65 mg per cu meter (10 ppm) in any eight-hour shift over a 40-hour work

TABLE 2.—*A Partial List of Occupations in Which Exposure to Xylene May Occur*

Adhesive materials workers
Aviation gasoline workers
Benzoic acid makers
Cleaning fluid makers
Histology technicians
Laboratory technicians
Lacquer and varnish workers
Leather workers
Organic chemists
Paint and glue workers
Phthalic anhydride makers
Polyethylene terephthalate film makers
Quartz crystal oscillator makers
Refinery workers
Semiconductor industry workers
Solvent materials workers
Synthetic textile makers
Terephthalic acid makers

week. However, the United States National Institute for Occupational Safety and Health (NIOSH) has recommended that the 10-ppm figure be reduced to 2 ppm.[7]

Carbon tetrachloride is found in the environment. Air samples in 42 locations in the Los Angeles basin contained an average of 1.4 μg per cu meter (0.22 parts per billion).[8] The compound has been found in rivers, lakes, drinking water and effluent water from commercial manufacturing sites and from sewage treatment plants. Tolerable residue levels have been established for crops and foods: for example, in raw cereals, 50 ppm; in milled cereal products to be used for baking, 10 ppm.

The mechanisms of the hepatotoxicity of CCl_4 have been examined carefully in animals.[9-14] These studies have not only described the pathophysiology of the hepatic injury but also have led by extrapolation to a knowledge of the mechanisms of toxicity of many other compounds. The extent of injury depends more on the dose of CCl_4 than on the sensitivity of the person exposed, and can be reproduced in many species. The characteristic pathologic feature in the liver is centrilobular necrosis. The injury that leads to cell death and the necrosis. The injury that leads to cell death and the process of necrosis (conversion of dead cells to debris) follows the metabolism of CCl_4 by cytochrome P-450-dependent monooxygenases in the centrilobular liver cells. As one chlorine atom or more are cleaved from the intact molecule during metabolism, electron-deficient and, therefore, electrophilic, reactive intermediates or free radicals are produced. If not scavenged by further metabolism or conjugation, the reactive metabolites can bind covalently to a number of critical molecules and either interfere with vital cell functions or cause lipid peroxidation of cell membranes, or both. Metabolic alterations in the liver cell that result from administering CCl_4 to rats include increased fat deposition, reduced rate of amino acid utilization, decreased membrane phospholipid exchange, altered mitochondrial respiration, depressed intracellular concentrations of adenosine triphosphate and increased cellular calcium content.

The cytochrome P-450-dependent monooxygenase system found in many organs consists of a number of different forms of cytochrome P-450, each with different substrate specificities.[15] The P-450's are distributed differently throughout the liver cell lobule. The relative localization of CCl_4 toxicity to the centrizonal area of the liver cell lobule presumably relates to the presence of a larger amount of a form of P-450 that metabolizes CCl_4 in this zone than in other zones.[16] The cytochrome P-450-dependent monooxygenases are part of an extremely dynamic system and their activity changes with a large number of endogenous and exogenous variables:[17] gender, age, diet, hormonal status, genetic, diurnal and pathophysiologic factors (such as liver disease), and effects of drugs and chemicals that can enhance or inhibit the activity of the monooxygenases. For example, rats pretreated with a low protein diet or inhibitors of P-450 metabolism are much less susceptible to the hepatotoxic effects of CCl_4 than those pretreated with compounds such as phenobarbital, that enhance P-450 metabolism.[18]

One fascinating aspect of CCl_4-induced hepatotoxicity in animals is the protection that a small nonlethal dose of the compound provides to an animal from the toxicity of a subsequent dose.[19] The protection may arise from suicidal inactivation of the P-450-dependent monooxygenase during its initial metabolism of CCl_4 and its subsequent inability to "activate" the second dose. Whether or not humans exposed chronically to CCl_4 or to other similar solvents are "tolerant" to repeated doses is not known.

Because continuous exposure of animals to CCl_4 results in hepatic cirrhosis, this compound provides a model for examining the effects of chronic hepatic injury in animals.[20] The compound also produces both benign and malignant liver tumors after oral or subcutaneous administration and inhalation. Presumably, reactive intermediates bind covalently to information-carrying molecules such as DNA, RNA or protein, the reactions involved in the initiation of carcinogenesis.

In humans, CCl_4 has produced hundreds of poisonings and fatalities after occupational exposure, suicidal ingestion or medical use of the chemical.[3,5,6] Most cases arose from the inhalation of the compound in workplaces where CCl_4 was used as a solvent or dry-cleaning agent. However, CCl_4 is absorbed through both the lungs and the skin. Stewart and Dodd[21] immersed volunteers' thumbs in CCl_4 for 30 minutes: the subjects exhaled concentrations of 3 mg per cu meter (0.64 ppm), and the expiration half time was about two hours. These data highlight the general principle that in the workplace both the lungs and the skin are major routes of absorption of chemicals. Ingestion is a less important route in the workplace unless food or cigarettes are contaminated.

The clinical sequence in CCl_4-induced poisoning is shown in Figure 1.[22] The acute effects on the central nervous system (dizziness, headache, confusion and coma) reflect the anesthetic properties of the haloalkanes or haloalkenes of which CCl_4 is an example. Gastrointestinal symptoms can occur after inhalation or dermal or oral exposure. In persons exposed to high

enough concentrations of CCl_4 to produce hepatic injury, anorexia, vomiting and malaise also develop between 2 and 24 hours after the exposure. Within that time, the liver and spleen may become palpable and extremely tender because of rapid enlargement. The patient may complain of pain in the right and left upper quadrants of the abdomen. Serum aminotransferase (transaminase) concentrations and prothrombin time rise as the clinical manifestations of hepatic injury develop. After 24 to 48 hours, sequelae of acute liver failure, such as hypoglycemia and encephalopathy, may appear. Concurrently, renal failure may develop. The renal abnormalities may result from the toxic effect of CCl_4 on renal tubular cells or from "functional" renal failure that accompanies acute liver failure.[6,23] If supportive measures can keep the patient alive until hepatic

TABLE 3.—*A Partial List of Important Chemicals, Their Use in the Workplace, and the Hepatic Responses Reported in Humans*

Chemical	*Uses*	*Hepatic Responses*
Arsenic and inorganic salts	As pesticides and alloys; in production of dyes, ceramics, drugs, fireworks, paint, petroleum, ink and semiconductors	Acute injury and death of parenchymal cells; cirrhosis; angiosarcoma
Beryllium	In alloys, cathode ray tubes, ceramics, electrical equipment, gas mantles, missiles, nuclear reactors and refractory materials	Granulomas
Carbon tetrachloride	As degreasers, fat processors, fire extinguisher, fumigant, production of solvents; in fluorocarbons, ink, insecticides, lacquer, propellants, refrigerants, rubber and wax	Acute injury and death of parenchymal cells; ? cirrhosis; ? carcinoma
Dimethylacetamide	As solvent	Acute injury and death of parenchymal cells
Dimethylformamide	As solvent, in manufacture of butadiene, drugs, dyes, petroleum resins, synthetic fibers	Acute injury and death of parenchymal cells
Dimethylnitrosamine	As solvent and in rocket fuel; in cancer research	Acute injury and death of parenchymal cells; ? carcinoma
Dioxane	As solvent, degreaser, cement component; in production of adhesives, deodorants, detergents, emulsions, fats, glue, lacquer, oil, paint, polish, shoe cream, varnish remover, waxes; in histology laboratories	Subacute injury of parenchymal cells
Pentachloronaphthalene	In electric wire insulation and some lubricants	Acute injury and death of parenchymal cells
Phosphorus (yellow)	In munitions, pyrotechnics, explosives, smoke bombs, fertilizers, rodenticides, bronze alloys, semiconductors, luminescent coatings and chemical manufacture	Acute injury and death of parenchymal cells
Picric acid (2,4,6-trinitrophenol)	As copper etcher, forensic and biology laboratory chemical; in batteries, colored glass, disinfectants, drugs, dyes, explosives, matches, photography chemicals and tanneries	Acute injury and death of parenchymal cells
Polychlorinated biphenyls	In cable insulation, dyes, electric equipment, herbicides, lacquers, paper treatment, plasticizers, resins, rubber, textiles, flameproofers, transformers, and wood preservation	Subacute injury of parenchymal cells, proliferation of smooth endoplasmic reticulum; ? cirrhosis; ? carcinoma
sym-Tetrabromoethane (acetylene tetrabromide)	As solvent and gauge fluid; refractive index liquid in microscopy	Acute injury and death of parenchymal cells
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Contaminant of commercial preparations of 2,4,5-trichlorophenoxyacetic acid, polychlorinated biphenyls and other chlorinated compounds	Porphyria cutanea tarda; proliferation of small endoplasmic reticulum and some forms of associated monooxygenase enzymes
Tetrachloroethane	As dry-cleaning agent, fumigant, solvent, degreaser; in production of gaskets, lacquers, paints, phosphorus, resins, varnish, wax	Acute injury and death of parenchymal cells
Tetrachloroethylene	As solvent, degreaser, chemical intermediate, fumigant; in production of cellulose esters, gums, rubber, soap, vacuum tubes, wax, wool	Acute injury and death of parenchymal cells
2,4,5-Trinitrotoluene	As explosive	Acute and subacute injury and death of parenchymal cells
Vinyl chloride	As chemical intermediate and solvent; in production of polyvinyl chloride and resins	Fibrosis, noncirrhotic portal hypertension, cirrhosis, angiosarcoma, carcinoma

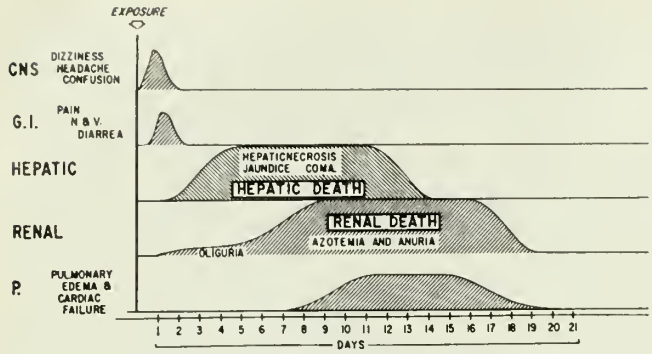

Figure 1.—Clinical sequence in acute carbon tetrachloride poisoning. (Reproduced with permission of the author and publisher from Zimmerman.[22])

and renal tubular cells regenerate, the ultimate prognosis for complete recovery is excellent, similar to the prognosis after acute ingestion of the hepatotoxin acetaminophen.

Whether or not there are any "antidotes" to acute CCl_4-induced hepatotoxicity in humans has not been established. Successful treatment with hyperbaric oxygen was reported recently in one patient, together with some experimental data in animals to support this form of therapy.[24] However, the therapy is by no means proved and in no way replaces full supportive care for hepatic and renal failure. Animals can be protected in several other ways from CCl_4-induced hepatotoxicity. For example, 16,16-dimethyl prostaglandin E,[25] chlorpromazine,[26] and cholestyramine and biliary diversion[27] protect against acute hepatic necrosis. These therapies have not yet been applied to humans.

Enhancement of the P-450 metabolism of CCl_4 by ethanol is one explanation for the well-documented synergistic effect between ethanol abuse and CCl_4 in humans.[6] Ethanol intake has been a concomitant factor in many of the human cases of CCl_4-induced hepatotoxicity, particularly in patients in whom both severe liver and kidney damage developed.[23] However, single doses of ethanol,[28] as well as other types of alcohol such as isopropyl alcohol,[29] also potentiate CCl_4 hepatotoxicity in animals. These potentiations must be due to other mechanisms.

Only anecdotal case reports have been presented as evidence that continuous exposure to CCl_4 causes cirrhosis.[3,5] However, this possibility is a cause for concern, particularly when one considers the synergistic effect of ethanol consumption on CCl_4-induced hepatotoxicity. Would hepatic cirrhosis be more likely to develop in persons who consume ethanol if they are exposed to a halogenated aliphatic hydrocarbon such as CCl_4 in the workplace? The answer is not known.

Again, only anecdotal reports suggest that CCl_4 can produce hepatocellular carcinoma in humans.[3,5] The evidence is still not sufficient to prove an association between the compound and hepatocellular carcinoma. However, in a retrospective study of causes of death in 330 deceased laundry and dry-cleaning workers who had been exposed to CCl_4, trichloroethylene and tetrachoroethylene, an excessive incidence of lung, cervical and skin cancer and a slightly excessive incidence of leukemias and liver cancer were observed.[30] The International Agency on Research in Cancer recommends that for practical purposes CCl_4 be regarded as a carcinogenic risk to humans.[5]

Vinyl Chloride

The fear that vinyl chloride might produce chronic liver disease and malignant tumors has been realized. As with CCl_4, a review of this chemical's toxicity highlights principles that apply to the toxicology of many workplace chemicals. Several reviews of its use and toxicity are available.[31-33]

Like CCl_4, vinyl chloride is a halogenated aliphatic compound. It is a colorless gas but is usually handled as a liquid under pressure. It is used in the production of resins such as polyvinyl chloride, as a chemical intermediate, as a component of propellant mixtures and as a solvent. The OSHA standard now sets a limit of 1 ppm over an eight-hour period and a ceiling of 5 ppm averaged over any period less than 15 minutes. However, problems with vinyl chloride were encountered before the permissible exposure limits were set. The recognition that an unusual type of hepatic fibrosis as well as angiosarcoma of the liver developed in persons who worked with vinyl chloride came after more than 30 years of steadily increasing production and use of enormous quantities of vinyl chloride.

Engineering surveys demonstrated that hundreds of thousands of workers had been exposed to high concentrations of vinyl chloride at various stages of its industrial production and use. Polymerization of the monomer vinyl chloride produces polyvinyl chloride, which is made into commercial or consumer products such as plastic pipe and conduit, floor cover, food wrap, and building and car interiors. These products may contain quite high concentrations of the residual monomer. In many polymers the residual monomer was present at 1,000 to 5,000 ppm by weight.[33]

Not only were workers engaged in the production of polyvinyl chloride or the use of vinyl chloride exposed to the concentrations of the compound, but also residents in areas near factories, people using vinyl chloride propellant sprays and possibly populations consuming food contained in plastics made with vinyl chloride. Vinyl chloride was also found in concentrations of 0.4 to 1.2 ppm in new automobile interiors. Vinyl chloride has been detected in cigarettes in concentrations of 5.6 to 27 nanograms per cigarette.[33]

It is instructive to examine in retrospect the information reported about the biologic effects of vinyl chloride.[34] Acute toxicity from vinyl chloride in guinea pigs, mice and dogs was reported in 1938. A report of cases of liver damage from vinyl chloride in humans was published in 1949. In 1961 chronic toxicity studies in several animal species showed that vinyl chloride at concentrations in the air above 50 ppm produced liver damage. Acroosteolysis, an unusual disease in humans, was associated with exposure to vinyl chloride in 1966. This disease is characterized by dissolution of the bones of the fingers and toes and vascular changes producing Raynaud's phenomenon. In

1970 the development of cancer in skin, lung and bones of rats exposed to vinyl chloride was reported. It was not until January 1974 that great interest in the compound was aroused. In that year a manufacturer of polyvinyl chloride and other polymers notified the public and appropriate state and federal agencies that three employees had died from angiosarcoma of the liver.[35] This tumor was unusual enough to make the association between vinyl chloride exposure and the tumor noticeable in such a small sample. The three employees had been exposed to vinyl chloride for up to 20 years. An immediate survey by NIOSH and similar agencies in other countries that used vinyl chloride confirmed the association between exposure to vinyl chloride monomer and development of this type of tumor and identified scores of cases.[36] These studies also found a consistent association between vinyl chloride exposure and tumors in sites other than the liver, not only in employees but also in populations living in areas surrounding vinyl chloride polymerization plants.[31] Angiosarcomas in vinyl chloride workers and animals were recognized virtually simultaneously.[31]

Similar to CCl_4, one mechanism of toxicity of vinyl chloride is through its metabolism by the cytochrome P-450 system to electrophilic intermediates. These intermediates react with nucleophiles (electron-rich donors) that either detoxify the intermediates or are critical cellular components. Detailed reviews of the pathologic lesions in animals and humans are available.[31]

Exposure of humans to vinyl chloride is associated with multiple systemic diseases including acroosteolysis, thrombocytopenia and liver damage. The latter can consist of parenchymal damage, fibrosis of the liver capsule and periportal fibrosis associated with hepatomegaly and splenomegaly, portal hypertension, hepatocellular carcinoma and angiosarcoma. Exposure to thorium dioxide (Thorotrast), a radiocontrast dye that is no longer used, and to inorganic arsenicals may be followed by development of the same tumors.[37] Arsenicals also produce the peculiar hepatic fibrosis associated with portal hypertension. Both vinyl chloride and the arsenicals induce proliferation of parenchymal and endothelial cells. Early abnormalities include sinusoidal dilation progressing to peliosis (blood-filled lakes within the liver lobule) and sarcomatous transformation of the lining cells of sinusoids and portal capillaries. Similar forms of sinusoidal dilation without angiosarcoma occur in women taking oral contraceptives and in men and women receiving large doses of anabolic steroids.[37]

Angiosarcoma of the liver is usually not recognized until within a few months of death. Whether or not earlier alterations in hepatic structure might be reversible if exposure to vinyl chloride is stopped is not known. An employee who is or was exposed to vinyl chloride in concentrations in excess of the now-recommended standard should have a complete history taken, including a history of liver disease and history of exposure to other potential hepatotoxic agents including alcohol, and a complete physical examination.[38] The full evaluation should be repeated every six months for an employee who has been working in vinyl chloride or polyvinyl chloride manufacturing for ten years or longer, and annually for all other employees. The liver function tests and bilirubin, alkaline phosphatase, serum aminotransferase and γ-glutamyl transpeptidase determinations should be done at the same time. If data suggest the presence of hepatic involvement, ultrasonography[39] or computerized tomographic scanning of the liver should probably be carried out to look for hepatic tumors.

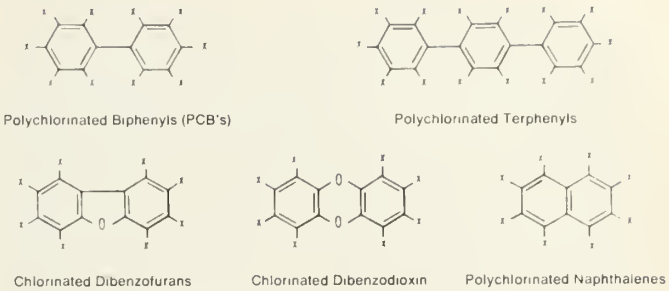

Figure 2.—General structure of polychlorinated biphenyls (PCB's), terphenyls, dibenzofurans, dibenzodioxins, and naphthalenes. X represents possible chlorine substituent. (Reproduced with permission of the author and publisher from Kimbrough.[40])

The experience with vinyl chloride highlights two principles paramount in occupational medicine—that occupational disease from some chemicals can be predicted in animal bioassays and that positive human epidemiologic data should not be necessary to conclude that a chemical poses a human risk. In contrast to our experience with vinyl chloride, the next chemicals discussed, the polychlorinated biphenyls (PCB's), provide an example in which production and use of the chemicals are being restricted in the workplace because of toxicities observed in experimental animals.

Polychlorinated Biphenyls

Biphenyl can be chlorinated by replacing one or more of its hydrogen atoms with chlorine. In the commercial synthesis of chlorobiphenyls, isomeric mixtures are produced that are referred to as polychlorinated biphenyls or PCB's. The biphenyl molecule, the numbering system and two examples of chlorobiphenyl compounds are shown in Figure 2.[40] Several reviews of their use and toxicity are available.[40-43] One common trade name under which commercial products have been marketed is Aroclor. The grades of Aroclor are designated by numbers such as 2521, 1221 and 1242. The last two numbers designate the percent by weight of chlorine in the mixtures. The first two digits indicate the type of product; for example, 12 equals chlorinated biphenyls and 25 equals blend of chlorinated biphenyls and chlorinated triphenyls. Commercial PCB products also contain contaminants such as dibenzofurans and naphthalenes (Figure 2). These impurities, which are often more biologically active than the PCB's themselves, have made interpretation of many epidemiologic studies of the toxicity of PCB's difficult.

Polychlorinated biphenyls were first produced commercially in the United States in 1929.[42] In 1970 pro-

duction had reached 80 million kg, and from 1929 through 1970 approximately 454 million kg of PCB's had been sold in North America. A second large commercial producer of PCB's, Japan, began production in 1954. By the end of 1971 approximately 54.4 million kg had been produced in that country; about 60 percent was exported to the United States and the remaining 40 percent was exported to Europe. The excellent thermal and chemical stability of PCB's led to their widespread use as insulating liquids in electrical capacitors, transformers and nuclear reactors and much of the accessory equipment. In addition, before 1971 PCB's were used in plasticizers, hydraulic fluids and lubricants, surface coatings, inks, sealants, adhesives, carbonless copy paper, pesticide extenders, for microencapsulation of dyes and as microscope immersion oils. These uses led to loss of about 40 percent of the PCB's into the environment. In the United States in 1971 the sole producer of PCB's limited their use to closed electrical systems so that release to the environment could be minimized.

Large-scale PCB contamination of cooking oil in Japan,[43] the death of 400,000 chickens in Japan from eating contaminated feed and destruction of 75,000 eggs in North Carolina because of contaminated chicken feed (400 ppm of PCB's)[44] led in part to voluntary restriction in the method of using these compounds. It had also become evident by 1968 that over the period of production and use since 1929, PCB's had become constituents of the human body. They persisted in the environment, accumulated in living tissue and were concentrated or biomagnified in the food chain,[40-42,44] similar to other organochlorine compounds such as the pesticide DDT. Many reports established "background" concentrations of PCB's in blood and tissues of human populations that had no occupational exposure to PCB's. Detectable residues were typically found in more than 50 percent of the persons tested and residues were found in human milk in several countries of Europe, North America and Asia. The reasons for the accumulation in tissues are that, like other heavy chlorinated compounds, PCB's are metabolized slowly, primarily in the liver, by hydroxylation and conjugation with glucuronic acid. Because of their lipophilicity, the major storage tissues for PCB are fat and liver. Apart from environmental contamination, PCB's had been proved to be carcinogens and had produced a number of other disturbing toxicities in animals. In 1976 the US Environmental Protection Agency banned the manufacture and sale of equipment containing PCB's and required the labeling of any existing equipment containing large quantities. As this equipment comes up for repair, the PCB's should be drained and replaced with a non-PCB oil. Now, NIOSH recommends an occupational environmental limit of 1.0 μg of total PCB's per cu meter of air and has outlined strict work practices for their handling and use.[45]

The PCB's have an extremely low acute toxicity in all animal species. The acute oral lethal dose for 50 percent survival in rodents given PCB's ranges from 1 to 10 grams per kg of body weight.

However, the array of adverse effects from chronic exposure to relatively low doses of PCB's observed consistently in animals includes acute and subacute hepatocellular toxicity, induction of the cytochrome P-450 system, induction of mitochondrial aminolevulinate synthetase producing various forms of porphyria, and endocrine, reproductive and immunologic abnormalities.[40-42,44]

The major changes in the liver of rodents fed PCB's chronically include enlarged livers, accumulation of lipid, proliferation of the smooth endoplasmic reticulum in the cytoplasm of centrilobular liver cells, fibrosis of bile ducts, and development of adenomas and carcinomas. The smooth endoplasmic reticulum contains the cytochrome P-450 system imbedded in lipid membranes. The PCB mixtures, powerful inducers of several forms of cytochrome P-450,[46] increase the activity of enzymes that metabolize drugs or environmental chemicals, including many chemical carcinogens. For example, in the Ames *Salmonella*/microsome mutagenicity test, the test bacteria are mixed with the microsomal fraction of rat liver. The liver activates many carcinogens by metabolism. To enhance the sensitivity of the test, the rats are pretreated with Aroclor 1254 or phenobarbital so that the P-450 metabolism of the carcinogens by the microsomal fraction is enhanced.[47] In animals, PCB's can potentiate the hepatic and renal toxicity of CCl_4 and other chlorinated hydrocarbons by enhancing their metabolism.[48]

As already mentioned, the PCB's are themselves mutagenic and carcinogenic in animals.[41] The predominant tumors are hepatocellular carcinomas. The carcinogenicity probably arises from metabolic products produced during the metabolism of PCB's by the cytochrome P-450 system. Primates are even more susceptible to development of PCB toxicities than rodents. The reasons for concern about the potential of PCB's to be carcinogens or to enhance the carcinogenicity of other workplace chemicals are obvious.

Polychlorinated biphenyls ingested in rice oil produced a serious human epidemic illness in Japan.[43] More than 300 patients became ill after ingesting a brand of rice bran oil contaminated with PCB's. The PCB's had leaked through the heat exchange unit used to heat the oil to remove odorous impurities before shipping. The PCB's were themselves contaminated with polychlorinated dibenzofurans and naphthalenes. The incident was referred to as the Yusho (oil disease) epidemic. The oil used for frying food, which may have altered the contaminating chemicals even further, was consumed from May through October 1968 and the first patient sought medical attention in June 1968. The health effects observed in that and other patients were chloracne, chromodermatosis, swelling of the upper eyelids and conjunctivitis, peripheral neuropathy and congenital abnormalities in babies born to women with Yusho. One report described a baby in whom Yusho developed from the PCB's contaminating breast milk. Of the patients examined early during the epidemic, 11 percent were jaundiced. The Yusho patients are now being followed to evaluate the potential of PCB's as

human carcinogens. However, how much the health effects observed in the Yusho epidemic can be extrapolated to occupational exposure is not clear for the following reasons. These people ingested a large amount of PCB's as opposed to inhaling or absorbing them through the skin. The exact chemical composition of the Yusho PCB's and their impurities is not known, except that dibenzofuran concentrations were high. Furthermore, frying of foods with rice oil could have produced new compounds that had their own toxicity or altered the toxicity of PCB's or their contaminants.

The health effects observed consistently in people exposed chronically to PCB's in the workplace are chloracne, contact or allergic dermatitis and brown chromodermatosis.[41,44] Reports from 1954 through 1976 noted abnormal liver function test findings in PCB-exposed workers. However, these studies did not control well for other chemical exposures, alcohol intake or other diseases. In 1981 Maroni and co-workers reported a study of 80 workers who were exposed to PCB's in a plant manufacturing electrical capacitors and transformers.[49,50] They measured PCB levels in the air and on the surfaces of machinery and tools and found that air concentrations were high. The major route of systemic exposure to PCB's was from percutaneous absorption of the chemicals. These investigators detected 16 people who had "pronounced hepatic involvement," determined from symptoms, clinical examination and laboratory tests. None underwent a liver biopsy. The 16 all were men and none had a history of excessive intake of alcohol or drugs. These data indicate that hepatic injury in humans from long-term exposure to PCB's should be regarded as a clinical problem. Alvares and co-workers[51] studied five persons who were occupationally exposed to Arochlor-1016 in a capacitor-manufacturing plant and showed that the clearance of antipyrine, a drug metabolized by the cytochrome P-450 system, was greater and the half-life of elimination shorter in these people than in non-PCB-exposed normal subjects. These data indicate that PCB's enhance the activity of the P-450 system in humans, probably by increasing liver content of the enzymes, in much the same way that they are potent inducers of cytochrome P-450's in animals.

Retrospective epidemiologic studies have not detected a significant excess of deaths from cirrhosis of the liver or carcinoma or reproductive effects in workers exposed for a long time to PCB's. However, the findings are not regarded as complete and prospective epidemiologic studies are still continuing. In view of the persistence of PCB's in the environment and in the body, and the irreversibility of some of their effects in animals, all attempts are being made to keep human exposure to PCB's at the lowest possible levels.

What should be done for a person who is exposed acutely to PCB's? For example, what measures would be appropriate if a capacitor exploded and a worker were drenched in oil? Immediate health effects are unlikely. However, the PCB's are absorbed easily through the skin and lungs. In such a case, the victim should remove all clothing, seal clothes in plastic bags and wash the skin thoroughly. If the eyes are contaminated, they should be flushed with water for 15 minutes. The spill area should be roped off to prevent anyone except those involved in the clean-up from entering. Appropriate local agencies should be contacted for information about the clean-up of the spill and disposal, storage and transportation of PCB's. Symptoms or signs of skin manifestations will be the first indication of PCB toxicity if the acute exposure was sufficiently massive. Because of the variation in background concentrations of PCB's between people, measuring blood or fat concentrations of PCB's to predict long-term toxicity is of no value.

Conclusions

This review has concentrated on compounds that appear to single out the liver as their target organ for toxicity. Many compounds do fall into this category, but the reader should remember that hepatotoxicity may be only one facet of a chemical's adverse effects. The sensitivity of the liver to the toxic effects of a chemical should warn physicians that other organs may also be affected. In animal studies the liver may be the first site of an injury that manifests in other organs as well. In humans the pesticide chlordecone not only produced hepatic injury but also neurologic and reproductive abnormalities.[52] Finally, 2-naphthylamine produces hepatocellular carcinoma in mice but bladder carcinoma in humans.[53] Thus, a chemical that produces its effects in the liver in animals, may manifest its toxicity elsewhere in humans.

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Occupational Work Evaluation of Patients With Cardiac Disease: A Guide for Physicians

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The capacity of cardiac patients to work in their occupations reflects a complex interaction of medical and nonmedical factors. Medical considerations include prognosis and the ability of patients to tolerate the physical, environmental and psychological aspects of their occupation. Nonmedical factors include the patient's satisfaction with the job, economic motivation to work and perceived risk of continued work. Patients' perceptions of their capacity to work and the risks of such work are especially important determinants of occupational work status after myocardial infarction and coronary operations. Symptom-limited treadmill exercise testing carried out three to four weeks after the acute event not only clarifies prognosis and quantitates functional capacity but helps patients to realistically assess their capacity for work. Approximately half of postinfarction patients are found by such testing to have a very low first-year mortality of less than 2 percent. Functional capacity is well maintained in these patients: they do not require formal reconditioning in order to resume their occupational work soon (three to five weeks) after infarction. Exercise testing performed soon after myocardial infarction and coronary artery operation affords practical guidelines for clearing a person to return to work and obviates much of the medically unwarranted disability that follows these events.

Evaluating the capacity of a patient with coronary heart disease to carry out occupational work often poses a difficult problem for the physician. This is especially true after myocardial infarction or coronary artery operation. The reason for the difficulty is that many complex medical and nonmedical factors influence any recommendation regarding these patients' return to work. *Medical factors* include the physician's medical evaluation of the patient's prognosis and functional capacity and the patient's perception of the importance of cardiac symptoms and the risk of resuming occupational work. *Nonmedical factors* include the psychological status of patients, their level of job satisfaction and their perception of the influence of occupational work on their health, the family's influence on any decision regarding return to work, economic factors that influence a cardiac patient to continue working or to retire, the employer's decision to retain or to replace the patient and ill-defined legal and administrative considerations that often impede a cardiac patient's return to work.

Although the physician may influence the *medical* aspects of the return-to-work decision, *nonmedical* aspects over which the physician exerts little control, such as the patient's job satisfaction, often dominate the process. In addition, no randomized clinical trial has ever compared the risk of earlier versus later return to work after a myocardial infarction or a coronary artery operation.

Confronted with this formidable array of uncertainties and conflicts, it is no wonder that physicians often feel frustrated in their attempts to classify and enhance their patients' occupational work potential. Further,

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there are few guidelines for providing clearance for cardiac patients to participate in occupational work. As a result, physicians' advice is often vague and unnecessarily conservative concerning work. This may lead to potential errors in management:

1. Low-risk patients are unnecessarily restricted from engaging in occupational work, often with harmful psychological, physical and economic consequences.

2. High-risk patients do not receive optimal diagnostic evaluation and therapeutic intervention before returning to work, with potentially lethal consequences.

We present a pragmatic approach to the issue of occupational work evaluation which addresses three major determinants of occupational work potential in patients with coronary heart disease: prognosis, functional capacity and psychosocial status. Although these principles are particularly germane to patients recovering from myocardial infarction, they are also pertinent to patients with chronic stable angina pectoris and to patients recovering from coronary operations.

Prognosis

Of the three determinants of occupational work potential, *prognosis* is preeminent because job-related cardiac events naturally dominate the decision making of the physician, the patient, the patient's family and the employer. Unless all four of these parties have reasonable confidence that the risk of occupational work is low, none is likely to favor resumption or continuation of work. For this reason it is imperative that all parties be well educated concerning the risk of subsequent cardiac events and the capacity of the patient to tolerate the physical, environmental and psychological aspects of his or her job.

Clinical assessment of prognosis in coronary patients has traditionally relied on features of the hospital course, the history, the physical examination, the chest roentgenogram and the resting electrocardiogram. More recently various specialized techniques have been used to evaluate prognosis, including treadmill exercise testing, phonocardiography, echocardiography, ambulatory electrocardiography, radionuclide angiography, thallium myocardial perfusion imaging, right atrial pacing and coronary arteriography. The role of specialized evaluation techniques in assessing the prognosis of postinfarction patients is not well established; not only are the results of these various techniques redundant with one another, but they are often redundant with information provided by the clinical assessment. In fact, most patients who suffer subsequent cardiac events can be identified on clinical grounds alone.

The major determinants of prognosis after infarction are the extent of myocardial necrosis and thus the residual cardiac reserve and the extent and severity of persistent myocardial ischemia. Ventricular function changes little after the first week following infarction[1] and the incidence of exertional angina, ischemic ST segment depression and thallium perfusion defects remains relatively constant or declines only slightly in the first three months after infarction.[2] Thus, there appears to be little reason to defer the exercise test evaluation past the third week following infarction.

Postinfarction exercise testing

We have previously documented the independent prognostic contribution of treadmill exercise testing carried out soon after myocardial infarction.[3] The rationale for doing this evaluation soon after infarction is that such testing may identify patients with a high risk of subsequent cardiac events within the following eight weeks, thus permitting potentially effective therapeutic intervention during this period. Treadmill-induced exercise abnormalities during early testing are also predictive of late recurrence—that is, recurrence within the first five years after infarction.

We have developed a simple approach to stratifying the risk of subsequent cardiac events, such as sudden cardiac death and recurrent myocardial infarction (hard medical events) during the first six months following infarction. A combination of *historical* characteristics including previous infarction or angina pectoris (or both) or recurrent ischemic chest pain in the coronary care unit and *clinical* characteristics such as congestive heart failure and unstable angina pectoris permitted the identification of patients with a particularly high risk of cardiac events within the next six months. In these patients, who made up 10 percent of the sample of 702 men with a mean age of 54 ± 6 years, the rate of hard medical events was 18 percent. In patients with adverse clinical characteristics only, who comprised 30 percent of the population, the rate was 6 percent to 8 percent.

Of the remaining 60 percent of patients considered medically eligible to undergo exercise testing three weeks after infarction, 50 percent actually underwent such testing. Their rate of hard medical events within six months was 4.4 percent: 3.9 percent in patients with a negative test and 9.7 percent in patients with a positive test (ischemic ST segment depression of 0.2 mV or more and a peak heart rate of 135 beats per minute or less). Of the patients undergoing testing, 90 percent had negative tests by this criterion. Very low-risk patients with negative treadmill tests made up 46 percent of patients 70 years old or younger and 53 percent of patients 60 years of age or younger.[4]

Postinfarction exercise testing has an additional and complementary role in low-risk patients beyond the definition of prognosis: it is also useful in formulating individualized *guidelines for physical activity* in these patients. With the advent of automation, functional capacity has greatly declined in importance as a determinant of occupational work potential: the proportion of patients carrying out "heavy" work is no more than 5 percent to 10 percent. Further, persons who exert heavy physical efforts on the job are generally younger than those afflicted with myocardial infarction. Finally, low-risk patients as defined by negative treadmill exercise tests have a well-preserved functional capacity.[5] Even in patients who received no formal recommendations for physical reconditioning, the functional capacity seven weeks after infarction was 8.2

±1.9 MET (multiples of resting energy expenditure).* This level was adequate for the performance of all but the heaviest occupational tasks. The spontaneous increase in functional capacity from 7 MET at 3 weeks to 9 to 10 MET at 11 weeks reflects primarily an increase in peak heart rate and in arteriovenous oxygen difference and possibly in stroke volume. We and others have found no substantial improvement in ejection fraction measured by radionuclide angiography at rest or during exercise or in reversible perfusion abnormalities by thallium imaging during the first three months after infarction.[2] Thus it appears that the increase in functional capacity following myocardial infarction reflects primarily "peripheral" adaptations rather than "central" changes in pump function. In fact, much of the restoration of functional capacity that occurs in the first month after infarction may reflect a restoration of optimal intravascular volume following a period of bed rest and restricted physical activity.[6] Our later experience with exercise conditioning indicates that low-risk patients may safely augment their functional capacity through individualized low-level physical activity at home. Thus, even those low-risk patients whose occupations entail relatively vigorous effort may require little or no formal reconditioning before resuming their occupational tasks.

Functional Capacity

Blue collar workers generally return to work later after infarction than white collar workers. There is little medical basis for such distinctions among low-risk patients. In fact, it seems clear that these descriptive classifications of occupational work tasks should be replaced by a *functional* classification that incorporates assessment of prognosis and functional capacity. Recent experience has provided new insights into the process of occupational work classification of cardiac patients. This experience suggests that the potential for *myocardial ischemia* and *left ventricular dysfunction* developing during occupational work may be a more relevant performance criterion than *peak oxygen transport capacity*. Myocardial ischemia and left ventricular dysfunction are major determinants not only of prognosis but of functional capacity. The relevant question for the clinician to ask is how best to detect these abnormalities during the various combinations of physical, environmental and psychological stressors entailed in occupational work.

Past efforts in work classification have emphasized *laboratory simulation* of the patient's work environment, but this is cumbersome and difficult particularly as a way of assessing psychological stress. Rather than attempting to simulate the work environment in the laboratory, we have chosen to evaluate the *peak cardiovascular response* to various combinations of physical and environmental stressors.

*MET is a term derived from the word "metabolic," which describes the energy cost of various physical activities. One MET—the energy cost of quiet standing—is approximately equal to an oxygen consumption of 3.5 ml per kg per minute. The MET convention provides a convenient expression of the intensity of treadmill effort. This permits comparison of exercise performance on different exercise protocols.

Testing Arm Ergometry Versus Leg Ergometry

Symptom-limited treadmill exercise testing has been particularly helpful in these efforts. While large muscle dynamic effort such as treadmill testing and bicycle ergometry does not simulate many of the physical conditions involved in occupational work—especially static and dynamic effort involving the arms—these test methods are nonetheless effective as a basis on which to evaluate the patient's ability to perform occupational tasks of various kinds. Such symptom-limited dynamic testing elicits a clinically maximal cardiovascular response that is likely to expose clinically important myocardial ischemia and left ventricular dysfunction. In comparisons of symptom-limited leg ergometry and symptom-limited arm ergometry, the former was more effective in eliciting myocardial ischemia.[6] Arm ergometry rarely exposed ischemic abnormalities that were absent during leg ergometry; in contrast, leg ergometry exposed myocardial ischemia in some patients with negative arm tests. This is because cardiac output, heart rate and systolic blood pressure and thus myocardial oxygen consumption are higher during symptom-limited leg ergometry than during symptom-limited arm ergometry. For the same reason, we never noted ischemic abnormalities during the static effort involved in handgrip or forearm lifting carried out in the resting position; peak systolic blood pressure rose substantially, but the heart rate and cardiac output were only modestly increased and failed to elicit an imbalance between myocardial oxygen supply and demand. Even the combination of static effort and symptom-limited dynamic effort was no more effective than symptom-limited dynamic effort alone in eliciting a peak cardiovascular response and exercise-induced ischemic and arrhythmic abnormalities in coronary patients.[8]

Testing Dynamic Effort in the Cold

Other investigators have noted a similar phenomenon for dynamic effort in the cold: the ischemic threshold of heart rate and blood pressure at which exercise-induced ischemic ST segment depression and angina pectoris appeared, the peak heart rate and systolic pressure and the incidence of angina pectoris were similar when symptom-limited dynamic effort was performed in ambient temperature and in a cold environment.[9] We have noted the same for symptom-limited dynamic effort in the postprandial state.[10] The cardiovascular response to *symptom-limited* dynamic effort tends to override the effects of additional stressors such as the postprandial state, cold and the performance of static effort, each of which substantially increases the heart rate and blood pressure during *submaximal* dynamic effort. It thus appears that although the peak workload and the workload at the onset of ischemic abnormalities are diminished by cold, food ingestion and static effort, the peak heart rate and systolic blood pressure and the incidence of cardiovascular abnormalities at peak effort are similar to those observed during symptom-limited dynamic effort alone. Further, the heart rate appears to "track" the onset of ischemic abnormalities as effec-

tively as the product of heart rate and systolic blood pressure.[10]

These findings considerably simplify the process of occupational work evaluation, for if ischemic abnormalities are absent during the symptom-limited dynamic effort of treadmill exercise or bicycle ergometry, they are also likely to be absent during most conditions encountered during occupational work. If such abnormalities are present during symptom-limited exercise, they tend to occur at a similar heart rate during repeated dynamic exercise testing and during circumstances in which cold, the postprandial state or static effort are superimposed upon dynamic effort.

Heart Rate

The heart rate and workload at which ischemic abnormalities appear during peak dynamic effort not only have prognostic significance but indicate whether these abnormalities are likely to appear during a patient's vocational activity. For example, exercise-induced angina pectoris appearing at a heart rate of 115 beats per minute is far more likely to interfere with a patient's activities than angina pectoris that appears at a heart rate of 145 beats per minute.

Heart rate is superior to tables of metabolic equivalents in regulating the intensity of occupational work in patients with coronary heart disease. Heart rate is an important determinant of peak cardiovascular response and hence of myocardial oxygen consumption and is therefore closely related to the onset of myocardial ischemia. Patients without exertional ischemic ST segment depression or angina pectoris therefore require no restriction of their physical activities, even within several weeks of myocardial infarction. In our experience it is distinctly unusual for a patient free of ischemic ST segment depression at three weeks to have clinically important ischemic ST segment depression of 0.2 mV or more during the next two months unless angina pectoris has appeared during this interval. On the other hand, patients with exertional ischemic ST segment depression or angina pectoris may not require restriction of their physical activity, especially if these abnormalities occur at a relatively *high* heart rate. If ischemic abnormalities occur at a relatively low heart rate, the more relevant concern is with prognosis, not with physical activity: such patients may benefit from further noninvasive or invasive diagnostic evaluation and from medical or surgical intervention.

Psychosocial Status

The third major determinant of occupational work potential is the patient's *psychosocial status*. This area is the most complex and most difficult to define in an individual patient. After myocardial infarction and, to a lesser extent, after coronary artery surgical procedures, patients and their families are often reluctant to allow resumption of occupational tasks for fear of precipitating myocardial infarction or death. Most patients and spouses perceive the heart as substantially weakened after myocardial infarction and prone to further damage by physical activity. Although these fears are usually medically unwarranted they may substantially limit a patient's occupational work potential.

Exercise testing is a useful technique for helping patients to form realistic expectations after infarction and coronary operations. The physical exertion of a symptom-limited exercise test carried out three to four weeks after an infarction or operation is usually the most strenuous physical effort the patient has undertaken since the acute event. Successful completion of this exercise test has a major immediate impact on patients' confidence in their capacity for physical activity. This confidence extends not only to the activities of rapid walking or bicycling, which are simulated by the exercise test, but to physical activities dissimilar to the test such as running, isometric effort and sexual activity. Patients' confidence increases further after a physician has explained the test results and provided specific guidelines for physical activity including resumption of occupational work.[11]

Postinfarction patients whose treadmill test findings are "negative" are reassured regarding their capacity to resume their customary physical activities. Patients with "positive" test results usually are reassured by learning that they may benefit from further diagnostic evaluation and from medical or surgical intervention. In either case, treadmill testing helps patients to form a realistic impression of their tolerance for the physical, environmental and psychological aspects of their usual activities. This may obviate much of the medically unwarranted disability that follows myocardial infarction and coronary surgical procedures.

Benefits of Early Return to Work

We have described the medical rationale for functional evaluation soon after a myocardial infarction or coronary artery operation and the interaction of prognosis, functional capacity and psychosocial status in determining a patient's occupational work potential. A major consequence of identifying low-risk patients is an earlier return to work for these patients—a consequence with major public policy implications. Although most patients ultimately return to work after heart attack, the duration of their convalescence is often excessive, at least in the low-risk subset. In our population as a whole, for example, the time at which patients return to full-time work is 81 $\pm$40 days. If the return-to-work decision were made solely on the basis of prognosis and functional capacity, it appears that the delay in return to work of low-risk patients could be halved.

A shortening of convalescence of this magnitude would substantially diminish the costs of disability, which are a large proportion of all costs related to myocardial infarction. Of the 500,000 Americans who survive a myocardial infarction each year, approximately 250,000 are previously employed men of whom half would be medically eligible to undergo early treadmill testing. Shortening the return-to-work time from 81 to 53 days in these 125,000 patients would reduce disability costs from approximately $1.25 billion to $632 million a year, even when the unit cost of tread-

mill exercise testing of $160 is considered. The safety of early exercise testing and an earlier return to work of this magnitude in low-risk patients are implicit in this model. For a patient's employer, an earlier return to work means less disruption of work in progress resulting in lower costs for temporary help and less lost productivity. For insurers, it means lower costs for disability insurance payments to beneficiaries. For a patient, it means less loss of income. It is also likely that patients who return earlier to work on the basis of a negative exercise test will experience a lower rate of premature—that is, medically unwarranted—retirement with further economic benefits to employers and to patients.

Attractive as these economic benefits may be to employers, insurers and patients, they will not accrue unless patients and their families, employers and physicians are reassured concerning the safety of earlier return to work. Our emphasis on encouraging low-risk patients to return to work is therefore a pragmatic one: the occupational disability of such patients is largely *behavioral* inasmuch as it is medically unfounded and can be largely obviated by effective early evaluation and encouragement—an approach that is relatively inexpensive and therefore likely to be cost-effective. In contrast, the disability of high-risk patients is largely *medical;* it reflects important degrees of myocardial ischemia and left ventricular dysfunction—conditions that often require intensive (and expensive) medical and surgical treatment.

Future efforts to diminish occupational disability after a heart attack must therefore proceed along two parallel paths: (1) to demonstrate to patients and their families and to employers and physicians the safety of early return to work and (2) to actively enhance patients' perceived ability to tolerate the various stressors of their occupational work. This activist approach is in contradistinction to the passive approach—that is, allowing many weeks for the turmoil of myocardial infarction to dissipate and then often transferring patients to "less stressful" jobs. Although myocardial infarction is certainly a traumatic event, we have been impressed by the resiliency and adaptability of postinfarction patients who receive early functional evaluation and counseling.

These patients want to know what caused their heart attack and what they can do to prevent a recurrence. For example, many of our patients have cited job stress as an important contributor to the initial infarction. We have provided these patients with programs of stress management that are oriented to coping with occupational stress. Nearly half of our patients were smoking before their infarction and most perceived that smoking contributed to their heart attack. We have provided specific information on how to stop smoking and have continued to support patients' efforts to stop smoking. Patients have been advised how to manage occupational stress and to stop smoking in the context of individually tailored physical activity programs. Participation in daily physical activity affords an opportunity for patients to model healthy behavior. This appears to reinforce confidence in their ability to resume their customary activities, including their occupational work. In other words, this skills-oriented approach helps patients to modify their perceptions of their health. Patients who have received training in stress management, smoking cessation and physical activity conditioning appear more confident about their capacity to lead a normal life. These perceptions appear to have a major bearing on patients' willingness to resume or continue their occupational work. Whatever means are ultimately found most effective for enhancing patients' perceptions of their capabilities, this is an important objective of patient management—one which has major potential for enhancing the functional effectiveness of patients with coronary heart disease.

Low-Risk Versus High-Risk Patients

We have emphasized the identification and management of low-risk patients. How do we manage high-risk patients? Is their prognosis worsened by occupational work? Do therapeutic interventions enhance their occupational work potential? The principles of occupational work evaluation are similar in all patients: those at a high risk on the basis of adverse historical and clinical characteristics, especially the presence of congestive heart failure and unstable angina pectoris, should be considered for further diagnostic evaluation and therapeutic intervention. Using a stepwise risk stratification procedure, we correctly identified 72 percent of cases in which reinfarction or death occurred during the first year after infarction: of patients who were correctly classified, 35 percent had adverse historical characteristics (prior infarction or angina or recurrent chest pain in the coronary care unit, most of whom also had clinical heart failure or unstable angina pectoris), 55 percent had adverse clinical characteristics (clinical heart failure or unstable angina pectoris without adverse historical characteristics) and 10 percent had an abnormal exercise test finding in the absence of adverse historical or clinical characteristics.[4] Once the highest risk patients have been identified on the basis of historical and clinical characteristics, the prognostic value of specialized evaluation techniques, including coronary arteriography, is bound to be small.[12]

Early evaluation of prognosis facilitates early definitive therapeutic intervention in high-risk patients: if subsequent infarction and death are to be prevented in these patients, it is important that intervention be provided early. Levine and associates have shown the safety and benefit of coronary artery operations carried out within 30 days after infarction in patients with refractory angina pectoris.[13] The efficacy of coronary surgical treatment in improving prognosis has yet to be established in patients who are asymptomatic or mildly symptomatic after infarction.[14] At present we advocate coronary arteriography for patients with moderately severe angina pectoris and for patients whose three-week postinfarction test results are positive to a pronounced degree. We do not advocate coronary arteriography for patients with mild angina pectoris or for those with negative treadmill tests because their first

year mortality is so low that they are not likely to benefit further from coronary artery operations. Using these criteria, it appears that fewer than a fourth of previously employed men 60 years old or younger would be candidates for coronary arteriography in the year after infarction.

Even if the prognosis of postinfarction patients can be defined with reasonable certainty, the influence of occupational work on prognosis is uncertain. The prognosis of patients who return to work is better than that of patients who do not—a reflection of more advanced disease in the latter.[14] There is a low rate of dropout from the working environment in patients who return to work after myocardial infarction: 4 percent to 6 percent within 12 months. There has been a presumption that a delay in return to work after infarction is in some way protective; that is, a return to work after three months is safer than an earlier return. Because the death rate is highest in the first three months after infarction, it is far more likely that the greater perceived safety of a three-month delay simply reflects the death of high-risk patients—deaths that could possibly have been prevented by earlier identification and therapeutic intervention. To determine whether early return to work influences subsequent outcome, a randomized clinical trial of medically comparable patients is necessary.

Cardiac symptoms do not represent an important limitation of occupational work potential: for example, many studies have documented a similar rate of employment in patients with and without angina pectoris. The widespread use of beta blockers and calcium antagonists is likely to further diminish the effect of symptoms on employment status. Even a coronary artery bypass graft operation, one of the most definitive types of treatments available for patients with coronary heart disease, does not appear to enhance employment status.[16] This is not because the surgical procedure fails to enhance functional status or to diminish symptoms, but because many other factors such as age, educational level and length of disability before the operation are even more important determinants of occupational work status. On the other hand, objective evaluation of cardiovascular status soon after a coronary artery surgical procedure and provision of explicit guidelines for physical activity, including return to work, are likely to augment the effectiveness of the operation in enhancing occupational work potential. This can be accomplished by exercise testing four to five weeks postoperatively. We have previously documented a large spontaneous increase in functional capacity after the procedure even in the absence of formal exercise conditioning.[17] These patients did not require formal conditioning in order to resume their customary occupational work.

Conclusions

The medical rationale for occupational work evaluation as presented here appears to have much potential for diminishing disability in low-risk patients after infarction but this potential has yet to be shown in a controlled clinical trial. Until such results are available, the principles of occupational work evaluation elaborated above will provide practical guidelines to physicians concerning work clearance for their patients with coronary heart disease.

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Male Occupational Reproductive Hazards

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Studies assessing reproductive function among male workers were rare in the United States before the discovery of sterility and infertility in 1977 among employees of a pesticide formulating plant in central California. Subsequently, the etiologic agent, dibromochloropropane (DBCP), has been shown in numerous studies of humans and animals to produce similar effects. While studies on the influence of workplace exposures to various chemicals on reproductive function have proliferated during the past five years, no other single agent has approached the dramatic effects exhibited by DBCP. Other agents that have been evaluated and have shown some adverse effects are reviewed critically. Studies of spontaneous abortion or congenital abnormalities in children of wives of men exposed to anesthetic gases and DBCP indicate that pregnancy outcome, as well as infertility and sterility, is an important outcome measure.

Concern about male reproductive hazards resulting from occupational exposures is relatively recent. Historically, research into occupational reproductive problems, either in men or women, has been inadequate, reflecting this lack of interest. Worker protection policies aimed at controlling this problem have been discriminatory, primarily directly aimed against one group—women—and have usually resulted in the exclusion of all women from certain jobs "for their own protection." For this reason, reproductive hazards have been considered primarily a women's issue.

Most studies concerning the effects of chemicals on human spermatogenesis have focused on two areas: (1) the therapeutic use of drugs as possible male contraceptives or as stimulators of sperm production in subfertile men and (2) potential spermatotoxic side effects of drugs administered for therapeutic purposes. However, not until the testicular toxicity of dibromochloropropane (DBCP) was recognized in chemical workers in 1977[1] did it become generally accepted that the male reproductive system can be adversely affected by occupational or environmental exposures to chemicals.

Most external agents known to alter testicular function are pharmacologic agents. These include various hormones (testosterones, progesterones, estrogens and prednisone); alkylating agents (cyclophosphamide, chlorambucil, doxorubicin and methotrexate); nitroamino compounds (nitrofuranes and nitropyrroles); dichloroacetyldamines, and antitestosterone agents (cyproterone acetate).[2] Of the few studies done on workplace exposures, none of the chemical agents investigated either before or after 1977 have had the pronounced effects of DBCP.

Dibromochloropropane

DBCP will be discussed in some detail because of its pronounced effects. A liquid nematocidal agent, it has been used since the mid-1950's. Its primary value was its effectiveness on perennial crops without damaging the plants. Common crops treated with the chemical in the United States included citrus, grapes, peaches, pineapple, soybeans and tomatoes. It was used on bananas in Central America and Israel. Since 1979 its only allowed use in the United States is for pineapples in Hawaii.

Initial Observations

In 1961 DBCP was shown in laboratory animals to be a mild skin and mucous membrane irritant, to cause hepatic and renal damage and to produce testicular

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atrophy. It was shown to be an animal carcinogen in 1973 and an in vivo mutagen in 1975,[5] as well as producing infertility and sterility in human males in 1977.[1]

The discovery of the adverse testicular effects in humans is interesting and shows why one must listen closely to patients. The problem was discovered by the workers of the California pesticide formulation plant, not by physicians or scientists. The number of workers in the agricultural chemicals department where DBCP was processed was small and the workers were young enough to actively want children. The workers noted there was a paucity of children fathered by the men after each had started to work in that department. After considerable discussion, one worker convinced five co-worker volunteers to submit semen samples for analyses; all were grossly abnormal (azoospermic or severely oligospermic [fewer than 20 million sperm cells per ml of seminal fluid]). These results were sent to me as a consultant to the local union, although I had not previously seen the men or known about the semen samples. When repeated sperm counts were similar to the original ones, the remainder of the workers who, at the time, worked with agricultural chemicals were examined. Of the 36 men examined (100 percent of the at-risk group), 11 had had vasectomies previously; thus only 25 submitted fresh semen samples. Nine were azoospermic, three were oligospermic and 13 were normospermic.

As a group, there were no other abnormal physical or laboratory findings, except for elevated levels of follicle stimulating hormone and luteinizing hormone for men with low or absent sperm counts. There was a direct correlation between length of employment in that department and abnormally low sperm count.

These initial data from the men in the plant who worked with agricultural chemicals led to a larger study of all of the plant employees. Careful assessment of the data from the first 36 examinations made it clear that there was no need for an exhaustive medical workup on each of the subsequent participants. Accordingly, an abbreviated medical history questionnaire and physical examination strategy were devised. The questionnaire focused on the genitourinary system and emphasized reproductive history.

Studies of Workers

Of the entire 310 men employed by the company, 196 were examined, including the original 36. Semen samples were obtained from 142 of the 196 men examined. Forty-five men had had vasectomies and nine declined to give a semen sample. Thirty-five men providing semen samples "never" had had exposure to DBCP, while 107 "ever" exposed provided semen samples. The median sperm count was 46×10^6 per ml for the group of 107 men ever exposed to DBCP and 79×10^6 per ml for the 35 men never exposed. The Kolmogorov-Smirnov test showed the exposed and non-exposed distributions to be dissimilar ($\alpha = 0.05$). In the larger study, the same was true.

Of the 100 chemicals used in the plant, four had been shown to be toxic to the male reproductive system. Due to the relative quantities of production, the agent considered most suspect in this facility was dibromochloropropane.[6] Based on the reported findings, the two producers of DBCP (Shell Chemical Company and Dow Chemical Company) conducted medical evaluations of their workers and found similar results.[7,8] The association between exposure to DBCP and testicular dysfunction was strengthened when it was found that the only common exposure among the workers at the three plants was DBCP.

Seven separate studies were done in 1977 and 1978 on male workers who had been exposed to DBCP. Not all of these studies have been published nor was the same methodology used in all of them. All, however, showed that occupational exposure to DBCP has disastrous effects on testicular function: 14.5 percent of the subjects were azoospermic and another 21 percent were oligospermic. Finally, not all of the men in all of the studies were currently exposed to DBCP at the time of the studies.[7-12] In addition to these studies, recent studies on factory workers in Mexico[13] and field-workers in Hawaii[14] and Costa Rica (R. Smith, MD, Medical Director, Castle and Cooke, Inc., oral communication, 1981) have shown similar results of testicular dysfunction.

Women

The reproductive effects of DBCP on women are essentially unknown; in the various studies too few women were employed in jobs with exposure to the chemical to make an evaluation possible. However, Kharrazi and co-workers evaluated pregnancy outcomes of married women employed as banana workers in 14 kibbutzim in the Jordan Valley of Israel.[15] The data showed an increase in spontaneous abortion among the wives after their husbands' exposure to DBCP. Before exposure, 6.6 percent of pregnancies resulted in spontaneous abortion compared with a 19.8 percent spontaneous abortion rate in pregnancies after exposure. Whether this represents an effect on the sperm cell or the developing embryo or fetus is unclear.

Biopsy Findings

Histological examinations from testicular biopsies of men exposed to DBCP have shown a selective decrease or loss of spermatogenic cells without any other consistent testicular defect. The presumed mechanism was a direct toxic effect on the primary spermatogonia. In severely affected men, the seminiferous tubules were devoid of spermatogenic cells with only Sertoli's cells remaining.[6,16] In the less severely affected, there was a decrease in the amount of cellularity within the seminiferous tubules. There was no evidence of inflammation. There was minimal evidence of increase in fibrosis and interstitial changes.

Follow-up

Follow-up of the men in three of the earlier studies has been reported. In one study group, all of the azoospermic men remained azoospermic.[17] Both Lanham[9] and Potashnik (Potashnik G, Yanai-Inbar I, Sober I: Recovery of human testicular function sup-

TABLE 1.—*Environmental Agents Causing Adverse Male Reproductive Effects in Humans*

Alcohol
Anesthetic gases
Carbon disulfide
Dibromochloropropane (DBCP)
Diethylstilbestrol (male offspring in utero exposure)
Estrogens (in oral contraceptive manufacturing)
Ethylene dibromide
Chlordecone (Kepone)
Lead
Marijuana
Radiation (ionizing)
Toluene diamine

pression caused by dibromochloropropane, unpublished data, March 1981) report recovery to normospermic ranges for some of the previously azoospermic men. All three follow-up evaluations have reported relatively quick improvement in oligospermic men after exposure ceases.

One study done several years after cessation of DBCP production showed no differences between exposed and nonexposed men. The authors interpreted the data as evidence of recovery from a temporary effect.[18] Two evaluations of pineapple workers six months after cessation of DBCP use showed no difference between exposed men and nonexposed controls.[19,20]

Other Agents

Table 1 shows environmental agents that have been shown to cause adverse male reproductive effects in humans. Some of these agents have shown only marginal effects; others have shown both positive and negative results, most likely representing difference in exposures. Most studies have been on semen.[2] Agents for which other parameters have been examined are discussed below.

While anesthetic gases have been studied for reproductive outcome in numerous studies, the reevaluation of the data from the United States and Great Britain of operating room-based physicians showed paternal exposure to be associated with an increase in birth defects among their offspring.[21] A recent study of semen quality among male anesthesiologists was negative.[22]

In male workers manufacturing oral contraceptives, gynecomastia, decreased libido and impotence have developed.[23] The changes are reversible with removal from exposure.

Studies on three separate chemical agents and a study of a mixture of three chemicals have been published and reported as negative: epichlorohydrin,[24] polybrominated biphenols,[25] para-tertiary butyl benzoic acid[26] and glycerine production products.[27]

Two studies on carbaryl, done primarily on the same population, showed no abnormalities in sperm count.[28,29] The latter study did show a significant decrement in normal sperm morphology. Further study is necessary to understand the morphology findings.

More recent studies on lead, ethylene oxide, glycol ethers, a variety of chemicals at a Bahamanian chemical plant, mercury oxide and other Health Hazard Evaluations by the National Institute of Occupational Safety and Health have been done, but are not yet published.

Another method of evaluating chemical effects on testicular function is to assess pregnancy outcomes in wives of the exposed men. In this situation, one is looking for spontaneous abortions, stillbirths or congenital abnormalities. Two such studies described earlier for anesthetic gases[21] and DBCP[15] were positive for congenital abnormalities and spontaneous abortions, respectively. Carmelli and co-workers (A case-control study of the relationship between exposure to 2,4-D and spontaneous abortions in humans, unpublished SRI International Report, 1981) reported no increase in spontaneous abortions among wives of men exposed to 2,4-D. Several other studies are currently being conducted. The proposed mechanism is a mutagenic effect on the sperm cell DNA, resulting in an adverse pregnancy outcome.

Reproductive studies secondary to workplace exposures of male workers have proliferated rapidly during the past five years. While many methodological problems still exist for these studies (a discussion beyond the scope of this review), one can only predict that many more such studies will be done in the future. While DBCP has clearly caused the most obvious effects, other agents are likely to be present and have yet to be discovered. The future of occupational reproductive studies appears to be unlimited.

A practical approach to help develop priorities in deciding which chemical exposure to study would be the use of animal data. The most important data would be those in which the animals' testicular function is adversely affected at dose levels that have little or no effect on other organ systems. The effects of DBCP in humans could have been predicted using such a measure.

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BOOK REVIEW

RECENT ADVANCES IN OCCUPATIONAL HEALTH—Edited by J. C. McDonald, MD, FRCP, FFCM, FFOM. Churchill Livingstone Inc., 1560 Broadway, New York, NY 10036, 1981. 292 pages, $40.00 (softbound).

This book, with its 24 topics discussed by 33 authors in only 292 pages, has something for almost everyone. Its prose is generally engaging and occasionally enlivened by charts, pictures, formulas and tables. Although styles and formats vary, they are not jarring; problems in each topic are often highlighted and conclusions summarized. The topics, which are both usual and unusual, could appeal to a variety of readers. Of greatest interest to clinicians would be the sections about work hazards, such as asbestos and other mineral fibers, microwave, deepsea diving, carcinogenic effects of metals, protection of workers involved in energy production and agriculture in the Third World. The sections on investigative methods and worker protection are both brief and basic and would probably be of greatest interest to professionals in training. Because of the compact coverage of a diversity of subjects (including social aspects), this volume may be of particular use to policymakers. It frequently points up controversies and frailties, especially in the section on investigative methods. Many of the numerous authors are well known in the field; information given is as up-to-date as any can be in a book; most of the articles have 30 or more references, and the index is good. The weaknesses are quite minor and mainly relate to the slight fustiness of the section on investigative methods and the limitation of some of the examples to Great Britain.

Overall, the volume should be of interest to those with an interest in or responsibility for occupational health practice or policies, and those who are casting about for some stimulation, a quick overview or good bibliographies.

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Health Effects of Shift Work

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More than 13.5 million American workers, close to 20 percent of the work force, are assigned to evening or night shifts. In some industries such as automobile, petrochemical and textile manufacturing the proportion of shift workers is greater than 50 percent. As the popularity of shift work and other "alternative work schedules" grows, concern is increasing over the disturbance created in the lives of workers and their families by these economically and socially useful innovations. Twenty percent of workers are unable to tolerate shift work. Daily physiologic variations termed circadian rhythms *are interactive and require a high degree of phase relationship to produce subjective feelings of well-being. Disturbance of these activities, circadian desynchronization, whether from passage over time zones or from shift rotation, results in health effects such as disturbance of the quantity and quality of sleep, disturbance of gastrointestinal and other organ system activities, and aggravation of diseases such as diabetes mellitus, epilepsy and thyrotoxicosis. Worker selection can reduce the number of health problems resulting from shift work. The periodic examination of shift workers is recommended.*

When working time for American workers was reduced from a 12-hour day, six-day workweek to an 8-hour day, five-day workweek, many felt that the ideal in work scheduling had been achieved. Since then, a number of factors have caused management in business and industry to change the times when their employees work. The primary factor has been economic. The high cost of capital equipment and the need to compete in worldwide markets have forced many companies to operate 24 hours a day, requiring back-to-back or overlapping shifts that fill the 24-hour period. Technology has also played an important role in this change, because modern processes that require continuity, such as steelmaking, pulp and paper production, and petroleum operations, require workers to be on the job 24 hours a day. Transportation has been another contributing factor. In heavily populated business and manufacturing centers, many companies have opted for alternative schedules that permit workers to start their jobs at different times to diminish traffic congestion.

In recent years, more emphasis has been placed on the psychosocial needs of the worker so that more and more workers are being permitted to choose the hours and times when they wish to work. As a result of the foregoing factors, we now have several work scheduling alternatives: the eight-hour daylight schedule, permanent off-hour shifts, rotating shifts that change from daylight hours to evening to night periodically and schedules arranged according to the choice of the worker.

Although alternative work schedules are generally well received by workers, some epidemiologists, sociologists and health personnel have raised questions as to whether these work schedules cause physiological or psychological changes in the workers.

The Biological Clock

One of the most important questions asked with regard to work scheduling is whether shift or rotational schedules will affect the internal rhythms of the body—the body's biological clock.

All organisms function according to internal rhythms that are synchronized by such factors as light or dark, summer or winter, clock time or social stimuli. The synchronizers are called *Zeitgebers* (from the German meaning "time-givers"). In plants and animals, the primary synchronizer is light (or the absence of it). With humans, light is also a synchronizer, but a relatively weak one. The most important synchronizers for humans are the awareness of clock time and social interaction. For example, with transmeridian flight and the

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resultant time changes, humans are desynchronized from their *Zeitgeber*, clock time; similarly, when cut off from social interaction with families or others, humans lose their *Zeitgeber*. In humans and most animals, the internal rhythms governed by the biological clock approximate a 24-hour period and consequently are called circadian rhythms (from the Latin *circa dies* meaning "about a day"). The knowledge we have of these rhythms has come from investigators working with animals or humans and (1) removing subjects entirely from the normal light/dark cycle, (2) lengthening either the light or dark cycle or (3) inverting the sleep/wake cycle.[1]

From such investigations, it has been determined that body temperature fluctuates according to a rhythm; the endocrine system changes rhythmically; the flow of urine is rhythmic; the absorption, effect, metabolism and excretion of many drugs are strongly rhythmic; and the cardiovascular, hematopoietic, respiratory, and autonomic nervous systems all exhibit rhythmic patterns.[2] When the phase of a synchronizer is shifted—for example, when the light/dark cycle is altered as in experimentation—the body rhythms either shift with the synchronizer or become desynchronized from the external environment (light, time, society) and tend to become desynchronized from each other. Thus, the body temperature rhythm may run on a different time schedule from the external synchronizers and from the endocrine or other systems.

Circadian Rhythms in Shift Workers

Rutenfranz and co-workers have concluded that "Perhaps the most important physiological problem regarding shift work, particularly shift work which includes night work, is the problem of the reentrainment [resynchronization] of physiological functions after a phase shift of working and sleeping times."[1] This conclusion has been supported by studies of animals[3] and humans under controlled environmental conditions.[4-6] In shift work, the waking and sleeping times are phase shifted while the dominant human *Zeitgebers* of clock awareness and social stimuli remain constant. When this situation occurs, difficulties may follow. Air travelers who pass through time zone changes experience the same problem.[7]

Laboratory experiments have indicated that shift schedules with single night shifts did not alter the circadian rhythm of body temperature significantly. However, in night shifts lasting from one to three weeks, there was a shift of phase in minimum body temperature, with the minimum shifting to the new sleep period after seven or more days.[1] Different physiologic functions reentrain at different rates. Phase shift of physiological functions with shift rotation approximate findings observed after transmeridian flight.[7,8] In general, a full day of recovery time is required for each hour of time zone change. This would suggest that a week is required to adjust the normal phase relationship of circadian rhythms after shift rotation.

Although the occupational medical community considers the physiological problems related to shift work to be of primary concern, shift workers themselves feel that psychosocial shifts create the greatest problems in their lives. Thus, they are more concerned with whether shift work will interfere with or disrupt family relations or their social lives. Consequently, any shift work arrangement designed to alleviate physiological problems may not be acceptable to the shift workers if it does not also take account of their family and social relations.

Shift Work and Health

The primary health risk factors of shift work are sleep disturbance and altered eating patterns.[1,2]

Sleep Disturbance

Sleep quantity and quality is often disrupted when the sleeping time is shifted from night to day. The length of time shift workers sleep is indicated by the following findings of Menzel: Morning shift workers average 7.5 hours of sleep and afternoon shift workers average 8.5 hours, but night shift workers average only about 4 to 6 hours.[9] It has also been found that 50 percent of day shift workers sleep seven to eight hours, but only 15 percent of night shift workers sleep that long.[10] Similarly, other investigators have found the mean length of night sleep to be 7.55 hours and the mean length of day sleep to be 5.56 hours, with the shortest length of sleep occurring in people who go to sleep at the end of the night (5.45 hours).[11,12] It is generally found that day sleep lasts no longer than seven hours.[13-15] Of course, the hours of sleep needed differ by person and by age because sleep requirements lessen as one grows older. Nonetheless, Rutenfranz and co-workers concluded that all persons need more sleep time than is possible with night shift work.[16]

Sleep problems in shift workers occur primarily because the sleeping period is transferred to a time of day that is not conducive to sleep either in terms of circadian rhythms or environmental conditions. In the latter regard, the principal complaints of shift workers is that their sleep is disturbed by noises from children and traffic.[16-20] Investigations have shown that sleep disturbances are reported by workers as follows:[21]

- day workers, 15 percent to 20 percent;
- shift workers not working night shifts, 5 percent;
- night shift workers, 10 percent to 80 percent;
- permanent night shift workers, 60 percent;
- former night shift workers during night shift scheduling, 90 percent;
- former night shift workers during new day shift schedules, less than 20 percent.

When Thiis-Evensen surveyed 9,000 shift workers, he found that 20 percent of the workers suffered from lack of sleep, with the major complaint being disturbance from noise.[22] Of those who had to sleep between 7 AM and 7 PM, 78.8 percent complained of noise, with frequent sources being children, road traffic, telephone ringing and aircraft. When the same subjects slept during the night, there were no complaints about children's

noise or telephones ringing, of course, but complaints continued, although to a much lesser degree, about noise from road traffic and aircraft. Thus, it is evident that night shift workers experience greater problems with sleep disturbance than other workers. Environmental conditions play an important role in this problem. Workers living on well-traveled roads or near airports and in homes that are not well insulated against noise are particularly subject to sleep disturbance.

The quality of sleep is also affected by night shift work. The quality of sleep is generally accepted to be indicated by the different sleep stages that have been identified by electroencephalograms.[23] There are five sleep stages: stages I, II, III, IV and REM (rapid eye movement), which follow each other successively. It has been determined that sleep time is divided 4.4 percent to 5.4 percent in stage I, 48.7 percent to 51.2 percent in stage II, 7.7 percent to 10.1 percent in stage III, 11.2 percent to 13.2 percent in stage IV, and 22.9 percent to 24.1 percent in REM sleep.[24,25] Age does not appear to lessen REM sleep, particularly during the normal working years, but from the mid-30s on, stage IV sleep decreases while stage I sleep increases.[26,27] If sleep disturbances occur in stage II or the REM stage, the quality of the sleep is substantially impaired.

Impairments in both the quantity and quality of sleep can impair well-being and, if the impairments are severe, can affect work performance and safety cognizance. Workers who have problems in any of these areas should be questioned about the quantity and quality of their sleep and the environment in which they sleep. Night shift workers should be particularly studied in this regard; if there is evidence of severe sleep problems, they may need to be transferred to another shift.

Disturbance of Eating Patterns

Shift workers, particularly night shift workers, have a higher incidence of gastrointestinal problems than day workers.[22,28-30] The frequency of digestive problems among shift workers suggests that eating habits may play an important role. Appetite disturbances have been found to occur as follows in the various worker groups:[21]

- day workers, less than 5 percent;
- shift workers not on night shifts, less than 5 percent;
- shift workers on night shifts, 35 percent to 75 percent;
- permanent night shift workers, 50 percent.

Disturbances in appetite and gastrointestinal problems in shift workers, particularly permanent night shift workers, may occur because of the change in normal eating times, the difficulty of obtaining hot, nutritious meals during the night shift and the inability to have social contact during mealtimes with family or friends. Although calorie intake is not lessened in shift workers, appetite disturbances may be related to a dislike of eating outside the customary social environment. Sleep disturbances may also play a part.

The foregoing factors can result in gastrointestinal complaints although other conditions, such as personality, stress on the job, coffee drinking, family problems and social difficulties must also be taken into account. The incidence of gastrointestinal problems in shift workers is as follows:[21]

- day workers, 10 percent to 25 percent;
- shift workers not on night shifts, about 17 percent;
- shift workers on night shift, 5 percent to 35 percent;
- permanent night shift workers, about 50 percent;
- former shift workers who left shift work for health reasons, 30 percent to 50 percent.

The foregoing figures do not show a clear differentiation of gastrointestinal complaints among various groups of workers. Nonetheless, shift workers with gastrointestinal difficulties warrant medical attention and workers with more serious illnesses may need to be transferred to permanent daytime work schedules.

Other Health Problems

Diabetes mellitus and epilepsy are health problems that can be exacerbated by shift work since both have been found to be rhythmic in nature.[2]

Periodic variations have been observed in persons with diabetes mellitus, including 24-hour rhythms in the excretion of citric acid and β-hydroxybutyric acid and the production of ammonia in the kidney.[31] These rhythms may affect the timing of insulin administration. Furthermore, in diabetic persons, regular food intake and correct timing of medication are highly important and cannot always be achieved under shift work conditions.[1]

Epileptic seizures have been found to follow a rhythmic pattern in terms of the time of day when they occur.[32] In one study of 110 epileptic patients, the investigators observed that the incidence of seizures rose steadily from 3 AM to a peak between 6 AM and 7 AM, with the second highest incidence being between 10 PM and 12 midnight.[33] A later study concluded that night shift workers suffering from epilepsy tended to have seizures during their customary sleep time.[34] Sleep disturbance, a primary problem of shift work, is also believed to increase the incidence of epileptic seizuers.[35]

Psychosocial Aspects of Shift Work

Shift work may result in psychosocial problems that can sometimes be more difficult than physiological problems. There are fewer difficulties when a shift worker socializes primarily with other shift workers or lives in a community where shift work is the predominant work form. If that is not the case, shift workers may feel isolated from friends and community because participation in social and community activities is limited by the hours worked. Family relationships also present a problem because other members of the family often live according to a different work/sleep schedule, particularly if there are minor children.

Shift workers complain more frequently of sex-related problems and disturbed relationships with friends.[1] However, shift work can have some positive psycho-

social effects. A shift worker, of course, has more leisure time during the day to spend with family or friends if the latter are not working during the daytime hours. Yet it should be noted that this free time accrues not only from the shift system, but also from the reduced amount of sleep experienced by shift workers. Many shift workers, however, resent the fact that they cannot attend theater or sports events or even watch their favorite television programs, and some are now requesting that the timing of union meetings, religious services, television programs, shops and libraries be adapted to their working needs.[1]

Performance and Safety in Shift Work

Performance on the job and safety awareness are important considerations with regard to shift work.

To date, the evidence as to whether or not performance is degraded among shift workers is inconclusive. It is well known that human performance follows circadian patterns.[36-38] Thus, it would appear that the same type of work undertaken by the same person at different times of the day would result in different outputs. It is difficult to undertake a conclusive investigation of work performance and decrements created by shift work. One study has concluded that performance differs between morning-oriented and evening-oriented persons.[39] This study suggested that morning-oriented persons performed well in the morning hours but exhibited performance decrements during the evening hours, while evening-oriented persons performed poorly in the morning hours but considerably better at night. This conclusion suggests the value of determining morning or evening orientation as a shift assignment consideration.

Safety among shift workers is another inconclusive area of research. One team of investigators, in a study of vigilance efficiency, found that differences by the time of day were statistically significant in only a minority of the cases.[40]

Circadian variations in accident occurrences have been investigated, but the findings were contradictory. In one survey of 11,000 workers in the mining and steel industries, accident rates were found to be higher in the morning and afternoon shifts than the night shift, but accidents during the night shift were more serious.[41] Some investigators have concluded that two accident peaks occur during daytime hours, one at 10 AM and the other at 4 PM.[42-44] Conversely, other investigators found that daytime accidents, when grouped by 15-minute periods, showed peak occurrence times at 9:30 AM, 11:45 AM and 2 PM.[45] Studies attempting to relate accidents to rest breaks were also ambiguous in their findings.

Future studies should take into account the temperament and background of the persons involved; environmental factors, such as heat and cold, whether the individual has had accidents away from work and the particular time during the shift when the accident occurred.[46]

Optimal Shift Work Scheduling

There is no optimal shift work schedule that would meet the needs of all production operations or the living and working conditions of all shift workers. It has been suggested that the following criteria are useful in judging the appropriateness of a shift schedule:[1]

- Single night shifts are to be preferred over consecutive night shifts because the former do not alter the circadian rhythms significantly whereas seven nights of shift work are required to recentrain these rhythms.[47-49] Similarly, for psychosocial reasons, shift workers should work no longer than one week on the shift without free time or a change of shift.
- Each night shift should be followed by at least 24 hours of free time. Sleep deprivation is the primary complaint of shift workers, and this problem may constitute a risk factor when extended over several days. To offset the harmful effects of sleep deprivation, shift workers should be given a suitable recovery period after each shift.[50,51] Moreover, a 24-hour break should be allowed for morning shifts where workers must start so early that their sleep is likewise impaired.
- The length of the shift should be based on the type of work to be done. Thus, shifts involving light work can be longer than those that require heavy physical or difficult mental work, but in neither case should shifts be longer than eight hours. The "compressed workweek," with its workdays of 10 and 12 hours, is increasingly stressful to older workers.
- The length of the shift cycle should not be too long (4 weeks, for example, is better than 40 weeks).[1,52] Moreover, if a rotational system is used, the shift should be rotated regularly so that workers can plan their family and social lives. A recent study found that rotation every 21 days was preferred over weekly rotation by the workers, and that rotation by "phase delay," from day to swing to night shift, combined with the longer rotation schedule, improved subjective estimates of worker satisfaction and health, resulting also in a decrease in employee turnover and an increase in worker productivity.[53]
- Workers on permanent shift work should be given as many free weekends as possible so that they may participate in at least some family and social functions.

Selection of Shift Workers and Health Monitoring

Workers should be carefully reviewed before being assigned to shift work because 20 percent of the working population cannot tolerate shift work.[1] There are few clear-cut criteria for selecting shift workers. Many areas, such as health effects and performance, require a great deal more research. However, present knowledge indicates that there are those persons who should not be assigned to shift work, and plant safety and health personnel should give careful attention to the following categories of workers:

- New employees younger than 25 years of age (particularly if living alone) and older than 50 should be selected with caution for shift work. If the over-50 worker

is experienced and well adapted to shift work, he or she should be allowed to continue shift work on a voluntary basis. A worker may be chronologically 50, but physiologically many years younger.

- Persons with a history of gastrointestinal disorders should not be assigned to shift work, since gastrointestinal function may be affected by the psychophysiological problems inherent in shift work, as well as the disruption of meal times and frequent inability to obtain hot, nutritious meals at off hours.
- Diabetic persons and those with thyrotoxicosis should not be assigned to shift work without careful medical monitoring because regular food intake needed by diabetic patients and appropriate therapeutic timing required by persons with either condition are difficult under shift work conditions.
- Those with epilepsy, similarly, should not be assigned to shift work without medical evaluation and continued attention because sleep deprivation increases the likelihood of seizures.
- People with sleep disturbance problems or emotional instability are poor candidates for shift work. These conditions are likely to worsen with circadian desynchronization.
- Workers who live in noisy areas, as on busy arterial streets or near airports, and those who have sleeping quarters that are poorly insulated against noise also are not good choices for shift work because they are more than likely to be deprived of sleep even under normal working conditions.

Shift workers should be given particular attention by the health personnel of their companies. A suggested program provides all potential shift workers with medical examinations before assignment to shift work, six months after assignment and regularly every two years thereafter. Shift workers older than 50, however, should be examined more frequently.

Conclusions

Study findings on shift work have been relatively inconclusive with regard to health, performance and safety effects of shift work scheduling. This is due to methodological limitations in field investigations, and is inconsistent with numerous clinical observations that shift work, particularly rotational shift work, is a significant source of occupational stress. In recent years the growing popularity of "alternative work schedules" has also resulted in significant increases in subjective health complaints and employee turnover for health-related reasons. These work schedules may, in time, result in aggravation of diseases whose circadian rhythmicity is affected by the circadian desynchronization resulting from shift rotation, sleep deprivation, prolonged work shift and a number of other variables. Age appears to increase the susceptibility of workers to the problems of circadian desynchronization. As the popularity of "alternative work schedules" grows, clinicians will need to consider the age of their worker patients, the demands of the occupation and the presence of such predisposing risk factors as sleep disturbance, emotional instability and diseases such as diabetes mellitus and epilepsy when asked to evaluate the prospect of shift work assignment.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Reconsideration of Biofeedback

QUESTION:

In your judgment, are there valid medical indications for the use of biofeedback? If so, under what circumstances would biofeedback be accepted therapy?

OPINION:

In the opinion of the Advisory Panels on Internal Medicine and Neurology, biofeedback has legitimate use as part of a medical treatment plan. There are valid medical indications for the use of biofeedback for conditions such as chronic muscle contraction headaches, certain mixed headaches (of muscular and vascular origin), migraine, chronic pain syndromes of muscular or vascular origin, and other psychophysiologic states where excess tension, stress and high autonomic arousal are part of the syndrome. Modest results have been achieved in patients with moderate hypertension.

Biofeedback for neuromuscular reeducation and organic disease problems such as convulsive states and ectopic beats should be considered investigational. Its role as an adjunct to more established management remains unknown at this time.

Biofeedback is only as effective as the skill of the therapist and the ability of the patient to learn the techniques of relaxation. Because the treatment works in a limited number of patients and has the potential for overuse, candidates for therapy must be well selected. As significant underlying psychological problems may arise during the course of therapy, biofeedback practitioners should be highly trained in the fields of psychology and counseling.

Occupational and Community Exposures to Toxic Metals: Lead, Cadmium, Mercury and Arsenic

PHILIP J. LANDRIGAN, MD, MSc, *Cincinnati*

Lead, cadmium, mercury and arsenic are widely dispersed in the environment. Adults are primarily exposed to these contaminants in the workplace. Children may be exposed to toxic metals from numerous sources, including contaminated air, water, soil and food.

The chronic toxic effects of lead include anemia, neuropathy, chronic renal disease and reproductive impairment. Lead is a carcinogen in three animal species. Cadmium causes emphysema, chronic renal disease, cancer of the prostate and possibly of the lung. Inorganic mercury causes gingivitis, stomatitis, neurologic impairment and nephrosis, while organic mercurials cause sensory neuropathy, ataxia, dysarthria and blindness. Arsenic causes dermatitis, skin cancer, sensory neuropathy, cirrhosis, angiosarcoma of the liver, lung cancer and possibly lymphatic cancer.

Toxic metals are ubiquitous in the modern industrialized environment.[1,2] Each year 1.3 million tons of lead,[3] 6,500 tons of cadmium,[4] 2,500 tons of mercury[5] and 24,000 tons of arsenic[6] are consumed in the United States. Also each year an estimated 100,000 tons of lead,[3] 5,500 tons of cadmium,[4] 2,000 tons of mercury[5] and 10,600 tons of arsenic[6] are released into air and water. Environmental concentrations of these metals have increased steadily since the industrial revolution, and in the past 40 years ambient levels of lead have risen especially rapidly due to the release into the air of several million tons of lead particulates from the combustion of leaded gasoline.[7] The concentrations of lead found today in urban residents of the United States are more than ten times greater than those of persons dwelling in the remote Himalayas[8] and orders of magnitude above those found in the skeletal remains of prehistoric man.[9]

Adults have their most serious exposures to toxic metals in the workplace. Not surprisingly, industrial workers are the subset of the adult population in the United States with the heaviest body burdens of toxic metals.[10] The major route of absorption of metals in the industrial workplace is by inhalation.[11]

Children are exposed to toxic metals from numerous sources. They inhale airborne metallic particulates and ingest metals dissolved in food and in drinking water.[3] In addition, because of their typically oral behavior, they are at risk of ingesting heavy metals from painted surfaces[12,13] and from contaminated dust and soil.[14] Further, children may be at risk of exposure to industrial metals—*in utero* if their mothers are employed in the metal trades,[15] through inhalation of contaminated air if they live near a smelting plant[16] or through exposure to parents who wear contaminated shoes and clothing home from a dusty workplace.[17]

Evaluation of a case of toxic metal poisoning requires that attention be directed not only to the presenting patient but also to the context in which the patient was exposed to the toxic metal. The sources of exposure must be determined and the pathways of absorption traced. The possibility of multiple additive sources must be considered. Such investigation is necessary not only for full understanding of the clinical case but, even more

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ABBREVIATIONS USED IN TEXT

ALA-D = aminolevulinic acid dehydratase
EDTA = ethylenediaminetetraacetic acid
EP = erythrocyte protoporphyrin
HANES II = Health and Nutrition Evaluation Survey

importantly, for the prevention of recurrent exposure in the affected patient and for prevention of poisoning of his workmates, siblings or neighbors.

Lead

Sources of Exposure

Occupational exposure to lead occurs in hundreds of industries. Among the more important are smelting, battery making, paint scraping, shipburning, soldering, stained glass manufacture, and brass and bronze foundry work.[18]

Children may be exposed to both high-dose and low-dose (that is, concentrated and diluted) sources of lead. Low-dose sources serve generally to increase baseline absorption and thus to reduce the margin of safety between background absorption and toxicity. Superimposed high-dose exposure accounts for most cases of symptomatic lead poisoning.

Lead-based paint continues to be the major source of high-dose lead exposure for children in the United States.[12] Although paint produced for household use must today (by a 1976 regulation of the US Consumer Product Safety Commission) contain no more than 0.06 percent lead by dry weight, interior paint manufactured before the 1940s in some instances contained more than 50 percent lead.

Lead paint poisoning classically occurs in children under the age of five years who live in deteriorated housing built before World War II.[12] Although most cases of lead paint poisoning occur in the "lead belts" of the older cities in the northeastern and north central United States, they have been reported in all regions of the country, including the far west, and in both urban and rural settings. Occasionally, lead paint poisoning has been reported in the children of relatively affluent parents who have moved into a city as "urban homesteaders" and inadvertently exposed their children to paint chips during household renovation. Increased lead absorption has also been reported in children exposed to chips of lead-based paint released into a community during the removal of paint by sandblasting from bridges and elevated expressways.[19]

Lead-glazed pottery, although not a widespread source of lead absorption, can on occasion release large amounts of lead into food and drink and has been responsible for outbreaks of serious poisoning.[20]

Airborne lead is generally a low-dose source of exposure. Automotive and industrial emissions are the major contributors to lead in air, and of the more than 100,000 tons of lead particles released into air each year in the United States, more than 95 percent derive from automotive emissions.[3] Studies of children living near freeways in New Jersey[21] and in California[22] have

TABLE 1.—*Blood Lead Levels in One- to Nine-Year-Old Children in Relation to Distance of Residence From a Major Roadway—Newark, New Jersey, 1971**

Distance of Residence From Roadway (feet)	*Number of Children*	*Distribution (%) of Blood Lead Levels*		
		40 μg/dl	*40-59 μg/dl*	*60+ μg/dl*
<100 ...	758	42.6	49.3	8.1
100-200 ...	507	72.4	24.2	3.4
>200 ...	3,961	68.4	26.9	4.7

*From Caprio et al.[21]

shown significantly higher blood lead levels in children living within 100 feet of major roadways than in those living at greater distances (Table 1). In those studies the children's blood lead levels were correlated with the average daily traffic volume on the roadways near their homes.[21]

Although industrial releases account for only a small fraction of airborne lead, these immobile sources can produce concentrated zones of high-dose exposure.[16] The worst such situation in the United States existed in the vicinity of a large lead ore smelter near Kellogg, Idaho.[23] In 1974, 99 percent of one- through nine-year-old children living within one mile of the Kellogg smelter had increased lead absorption (blood lead levels of 40 μg per dl or above) and 22 percent had blood levels diagnostic of lead poisoning (levels of 80 μg per dl or above).[23]

Lead contained in dust and soil is also generally a source of low-dose exposure, although near smelters the dust lead concentration may be as high as 10 percent by weight.[23] Precipitated particles of airborne lead are the major contributor to the lead found in dust and soil; in urban areas, flaking paint adds an additional amount. Lead deposited in soil tends to remain in the topmost centimeter and not to migrate downward. In general, lead in dust and soil appears to be responsible for elevations in children's blood lead levels above background when the concentration of lead in the dust or soil exceeds 500 to 1,000 ppm.[24]

Lead workers' children may be exposed to lead dust transported home from the workplace on workers' shoes and clothing.[17] In an evaluation of lead exposure in workers' children in Tennessee a close correlation was found between children's blood lead levels, the severity and duration of parental lead exposure, and the lead concentration of household dust. In that episode, 38 (41.8 percent) of 91 workers' children had elevated blood lead levels, and 10 required treatment for lead poisoning.[17] Under regulations set forth in 1978 by the Occupational Safety and Health Administration, industries using lead are now required to provide changing and showering facilities for their workers.[15]

Lead in food and drinking water, although almost never responsible for lead poisoning, is a ubiquitous source of low-dose exposure. Canned foods may have a particularly high lead content, because lead may be leached from the seams of soldered cans.[25]

Lead fumes, produced by the burning of lead batteries in home stoves to generate heat during the winter,

is a recently rediscovered source of childhood lead poisoning.[26] Lead exposure from battery burning was a serious cause of lead intoxication during the Great Depression[12] and may increase again in frequency if fuel prices continue to rise.

Toxicity

Lead toxicity is evident principally in three organ systems: the red blood cells and their precursors, the central and peripheral nervous system, and the kidneys. Lead has also been shown to have adverse effects on reproduction in both males and females[27] and has been shown to be a potent carcinogen in three animal species.[28]

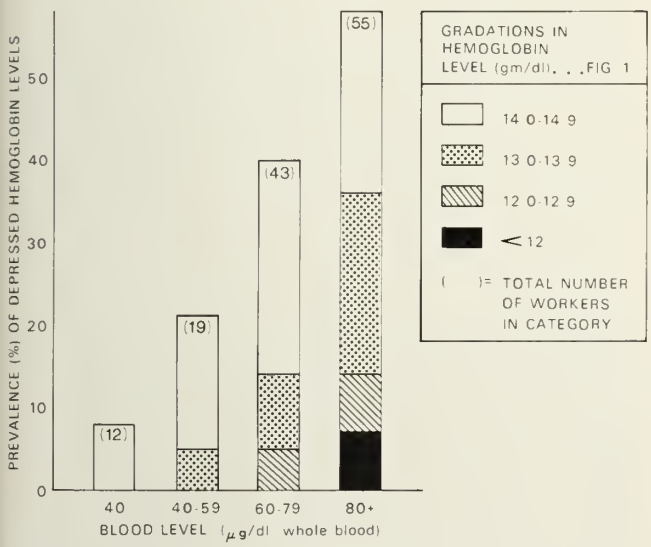

Figure 1.—Prevalence of depressed hemoglobin values by blood lead level in adult workers—United States, 1975-76 (adapted from Baker et al[29]).

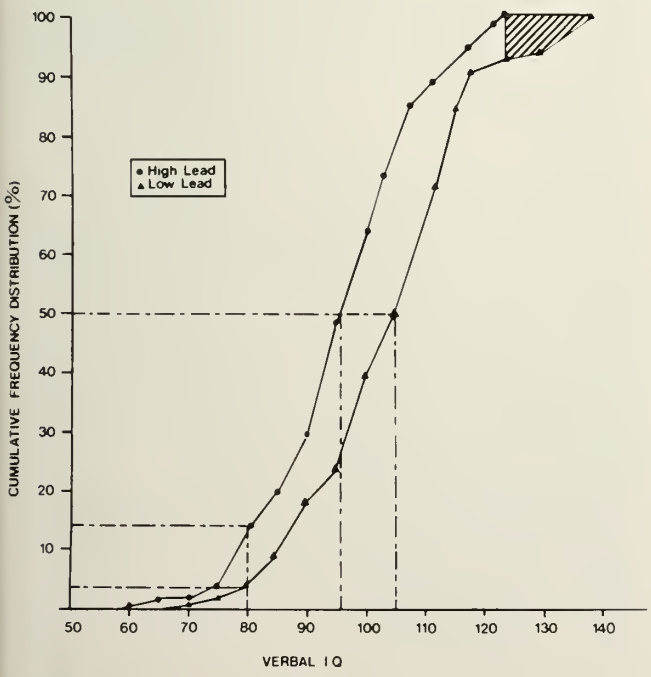

Figure 2.—Cumulative frequency distribution of verbal IQ scores in subjects with low or high levels of lead (adapted from Needleman et al[34]).

Anemia is the most serious manifestation of the hematologic toxicity of lead. Among the children who lived near the smelting plant in Kellogg, Idaho, 17 percent of those with blood lead levels of 80 μg per dl and above had hematocrits of 33 percent or below, whereas only 1.6 percent of children with blood lead concentrations below 80 μg per dl had depressions in hematocrit.[23] Among adult workers, anemia first becomes evident at blood lead levels between 40 and 60 μg per dl and increases in frequency and severity with increasing lead absorption (Figure 1).[29] The anemia of lead poisoning is occasionally accompanied by basophilic stippling of the red blood cells. Stippling is, however, an inconstant feature, and its absence does not exclude a diagnosis of lead poisoning.[13]

The anemia induced by lead may be either normochromic or hypochromic and is often associated with an increased reticulocyte count. It is caused principally by impairment of heme biosynthesis, but an increased rate of red blood cell destruction may also occur. At blood lead levels as low as 10 μg per dl, lead begins to inhibit the cytoplasmic enzyme delta aminolevulinic acid dehydratase (ALA-D) in the heme biosynthetic pathway; ALA-D inhibition is virtually complete at lead levels of 70 to 90 μg per dl.[30] Also at blood lead levels of 15 μg per dl in children and of 25 to 30 μg per dl in adults, lead begins to inhibit the mitochondrial enzyme ferrochelatase, which is responsible for catalyzing the transfer of iron from ferritin to protoporphyrin to form heme.[31,32] Ferrochelatase inhibition causes the metabolic intermediate erythrocyte protoporphyrin (EP) to accumulate to excess in red blood cells. EP elevation is thus a measure of both lead absorption and toxicity. Close correlations (as high as 0.91 in a steady state of exposure) have been noted in both adults[29] and children[23] between blood lead levels and EP concentrations.

In the peripheral nervous system, lead causes segmental demyelination. In extreme cases, this demyelination produces palsy of the wrist or ankle extensor muscles to cause "wrist drop" or "ankle drop." At lower levels of exposure, insufficient to produce overt symptoms, lead has been shown in both adults and children to produce a dose-related slowing of motor nerve conduction velocity.[23,33]

In the central nervous system, high doses of lead cause encephalopathy characterized in the most severe cases by coma, convulsions and death.[12] At lower levels of exposure, lead has been found to cause subtle but apparently irreversible deficits in intelligence, behavior and school performance.[34-39] In a carefully controlled epidemiologic study, Needleman and co-workers[34] found that clinically asymptomatic children with elevated body lead burdens had on average a four-point deficit in mean verbal IQ score as compared with children with lower lead burdens. Further, this four-point shift in mean IQ was found to be associated with a tripling in the number of children with IQ scores below 80 and also with a significant reduction in the number with

IQ's in the superior range (about 125)[35] (Figure 2). Similar results have been reported in studies in the United States by Landrigan and associates,[36] in Germany by Winneke and colleagues,[37] and in Britain by Yule and co-workers.[38]

The renal toxicity of lead is incompletely defined. Animal and human studies suggest that the proximal tubular lining cells are the tissue in the kidneys most sensitive to lead.[31] The first demonstrable renal effect of lead is the formation in these cells of densely staining intranuclear inclusion bodies.[31] Generalized aminoaciduria is another feature of early lead nephropathy in both children and adults. With continuing high exposure to lead, such as may occur in the industrial setting, various irreversible abnormalities in renal function become evident, including decreased glomerular filtration and decreased tubular concentrating ability.[29,40] Hyperuricemic gout, caused apparently by lead-induced impairment in the tubular secretion of uric acid, has been noted in a high proportion of cases of lead nephropathy.[41] The end-stage of lead nephropathy is chronic renal failure, characterized pathologically by interstitial fibrosis and by atrophy and cystic dilatation of the tubules with relative sparing of the glomeruli.[31] Excess mortality from chronic unspecified nephritis has been observed among lead smelter and battery workers in the United States.[42]

Evaluation and Diagnosis

The symptoms of lead toxicity are nonspecific.[12] Nausea, vomiting, diarrhea, and constipation are commonly reported.[29] Abdominal colic is a classic symptom, and can on occasion be so severe as to mimic symptoms of acute abdominal conditions that require operation. Tremor and muscle weakness have been noted. Frequently, symptoms consist only of fatigue, insomnia, irritability or headache.

A high index of suspicion is the essential prerequisite for making a diagnosis of either increased lead absorption or lead poisoning. Because none of the clinical features (except the inconstant finding of red blood cell stippling) are at all specific for lead intoxication, the diagnosis depends upon finding an elevated blood lead or EP level.

In children, the following diagnostic criteria have been developed:[13]

- *An elevated blood lead level,* which reflects increased absorption of lead, is defined as a confirmed concentration of lead in whole blood of 30 μg per dl or greater.
- *Lead toxicity* is defined as an EP level in whole blood of 50 μg per dl or above.
- *Lead poisoning* exists when a child has two successive blood lead levels of 70 μg per dl or greater and an EP level of 250 μg per dl or above, or both, in either the presence or absence of clinically evident symptoms.

In adults, whole blood lead levels of 40 μg per dl and above are considered to represent increased lead absorption.[15] Under regulations set forth by the Occupational Safety and Health Administration, adult workers with blood lead levels of 50 μg per dl or above must be removed from occupational lead exposure until their blood lead levels have fallen to below 40 μg per dl.[15]

Measurements of lead concentration in hair and in urine have not proved to be reliable indicators of lead absorption or toxicity, and a diagnosis of increased lead absorption or lead poisoning cannot be based on unsupported data from analysis of hair or urine for lead.

Chelating agents, such as calcium EDTA, which have proved extremely useful in the treatment of lead poisoning,[43] can also be administered diagnostically in a single intravenous dose to assess the mobile or potentially toxic fraction of the total body lead burden.[13] The EDTA mobilization test has no place, however, as a primary screening instrument because it involves administration of a drug with potential renal toxicity. Instead, use of this test should be restricted to confirmation in carefully selected cases of the results of blood lead and EP screening.[13]

Chelating agents have not been shown to restore subtle neuropsychological deficits in children chronically exposed to lead.

Measurement of nerve conduction velocity has also been used as a screening evaluation for heavy metal toxicity. However, numerous factors other than toxic metals, including trauma, diabetes, renal disease, chronic alcoholism and metabolic disorders, can influence motor nerve conduction velocity. Thus a finding of decreased nerve conduction velocity, unsupported by other measures of increased absorption of toxic metal, cannot by itself support a diagnosis of lead or other metal intoxication.

Recently, it has been shown that bony lead stores can be accurately measured by the technique of x-ray fluorescence analysis.[45] This noninvasive technique may gain wide acceptance in the future as a means of assessing lead burden.

Cadmium

Sources of Exposure

Cadmium is used in the manufacture of storage batteries, pigments, jewelry, electroplated materials and neutron absorbers in nuclear power plants.[4] Occupational exposure to cadmium can occur during its extraction and smelting or in the manufacture and use of materials containing the metal.[46] Because cadmium and lead frequently occur in the same ore bodies and have many similar uses in industry, exposure to cadmium is frequently accompanied by lead exposure.

Although cadmium is not so extensively dispersed in the environment as lead, community residents may be exposed to it by many of the same routes as they are to lead. Cadmium is released into the air by smelting plants, particularly by zinc and lead smelters. Near such plants, cadmium levels have been found to be high in air, dust and surface soil, and children living near zinc smelters have been shown to have significantly elevated body burdens of cadmium.[44] Cadmium may also be

released into the air at scrap recycling plants,[47] either from the burning of cadmium batteries or from the heating of plastics that contain cadmium as a pigment or stabilizer. Cigarette smoke contains measurable amounts of cadmium, and children living in the same households as smokers have significantly higher blood cadmium levels than the children of nonsmokers.[48] Children may be exposed to cadmium in foodstuffs, particularly in vegetables grown in soils enriched with sewage sludge; sewage sludge used as fertilizer has been shown to have a high cadmium content.[49]

Toxicity

Acute oral exposure to cadmium resulting from the use in food preparation of electroplated ice trays or pitchers coated with cadmium can cause gastrointestinal poisoning characterized by vomiting, diarrhea and crampy abdominal pain of sudden onset.[1] Acute exposure to airborne cadmium, as has occurred among persons fabricating jewelry with cadmium solder, produces a reversible syndrome of acute respiratory irritation characterized by conjunctivitis, rhinitis, anosmia, dyspnea and chest pain.[50]

The principal chronic toxic effect of cadium is on the kidney. Chronic exposure produces proximal tubular dysfunction, characterized initially by proteinuria, in particular by excretion of the low-molecular-weight protein, beta-2-microglobulin, and followed eventually by renal failure.[51] In populations of older adults in Japan chronically exposed to industrial cadmium effluents in contaminated rice, cadmium was found to be the cause of an acquired renal Fanconi's syndrome with severe osteomalacia termed itai-itai disease.[52] Chronic inhalation exposure to cadmium has been associated with development of emphysema. In occupationally exposed populations, cadmium has been associated with the development of cancer of the prostate and possibly of the lung.[53]

Evaluation and Diagnosis

Cadmium is extremely persistent in the human body, and its biologic half-life in humans has been estimated to be 17 to 33 years.[51] Most absorbed cadmium accumulates in the renal cortex.

Cadmium that has been absorbed in the recent past is most accurately assessed through measurement of the cadmium concentration in whole blood.[54,55] Although analytical results vary from study to study, it appears on the basis of best current techniques that the mean whole blood cadmium concentration of persons without occupational or unusual exposures is approximately 0.25 μg per dl, and that no more than 2.5 percent of persons in any population would be expected to have a blood cadmium concentration above 0.7 μg per dl. Thus the occurrence of a confirmed blood cadmium concentration above 0.7 μg per dl deserves careful investigation.

Measurement of urinary excretion of cadmium has also been used to assess cadmium exposure. However, the urine cadmium level appears more to reflect cadmium-induced renal tubular injury than cadmium absorption, and the concentration of cadmium in urine does not generally begin to increase above background until some degree of tubular injury has occurred.[51]

Determination of the urine concentration of beta-2-microglobulin by radioimmunoassay in persons exposed to cadmium is a useful confirmatory evaluation. The results of this test can be used to evaluate the presence of early cadmium-induced renal dysfunction.[51]

Determination of the cadmium content in hair has also been used to estimate cadmium exposure. However, this analysis does not distinguish externally deposited from systemically absorbed cadmium, and has not proved as reliable as the blood cadmium determination as an index of exposure.[50] A diagnosis of cadmium absorption or intoxication cannot be based on an unsupported hair cadmium determination. Diagnostic chelation has no role in the evaluation of cadmium absorption and has, in fact, been reported anecdotally to worsen the prognosis in cadmium nephropathy (H. Blejer, MD: personal communication, 1982).

Measurement of the cadmium content of the renal cortex by partial body neutron activation analysis[56] appears to be a promising noninvasive technique for evaluation of the body burden of cadmium and for relating body burden to external exposures as well as to pathologic outcomes.

Mercury

Sources of Exposure

Two forms of mercury with differing chemical and toxicologic properties are used commercially in the United States. Inorganic or elemental mercury is almost entirely an industrial poison, and is encountered by miners, smelter workers, mirror makers, mercury battery makers, instrument makers, jewelers, photographers, dentists and dental assistants.[57] Also children who play with droplets of metallic mercury may be at risk of exposure to mercury vapor.

Organic compounds of mercury, in particular the methyl and ethyl mercurials, are used as pesticides and as antifungal seed dressings. Thus organic mercury poisoning has occurred among pesticide formulators and seed handlers.[58] Much greater attention has, however, been directed to widespread outbreaks of organic mercury poisoning that have occurred in community populations as a result of their consumption of mercury-contaminated foodstuffs.[59] Major epidemics have occurred in Minamata Bay, Japan, where exposure resulted from ingestion of contaminated shellfish,[60] and in Iraq,[61] where exposure was caused by consumption of seed grain treated with mercurial fungicides.

Toxicity

The cellular mechanisms of mercury toxicity are poorly understood. Biochemical studies indicate, however, that the mercuric ion has a high affinity for sulfhydryl (-SH) groups in cellular proteins and that through reaction with sulfhydryl groups mercurial compounds can inhibit a wide variety of enzymes and also

disrupt membrane functions (active transport and permeability).[59]

Clinical Features

Acute absorption by inhalation of high doses of metallic mercury vapor causes symptoms of pulmonary irritation and encephalopathy. Deaths from this syndrome have occurred among children who threw globules of mercury on a hot stove to watch the droplets disappear. Acute oral exposure to inorganic mercury, which usually occurs as the result of attempted suicide, can cause a syndrome of gastroenteritis with abdominal pain, nausea, vomiting and bloody diarrhea; severe renal impairment leading to uremia frequently ensues.[57]

Occupational exposure to inorganic mercury is usually more chronic in nature, and the onset of toxicity is insidious. Inorganic mercury typically produces a syndrome of dermatitis, gingivitis, stomatitis and tremor, together with central nervous system dysfunction.[63] The neurological symptoms include irritability, pathologic shyness and the loss of attention span, memory and intellect and are collectively referred to as erethism. Lewis Carroll's mad hatter in *Alice in Wonderland* exhibited the symptoms of erethism, presumably as the result of his exposure to inorganic mercury in the old process of carroting felt in hat manufacture. Nephrosis may occasionally occur as a late result of chronic exposure to inorganic mercury. Today the full syndrome of inorganic mercury poisoning is seldom seen, but any of its components may be encountered in occupationally exposed groups.[57]

Poisoning by the organic compounds of mercury produces an almost purely neurologic illness.[64] Early symptoms include paresthesias, perioral numbness and other signs of sensory neuropathy. With continued exposure, the syndrome progresses to an almost pathognomonic triad of ataxia, dysarthria and visual field constriction. A devastating neurologic syndrome of congenital organic mercury poisoning has been observed in the children of women exposed to organic mercurials during pregnancy.[60]

Evaluation and Diagnosis

Recent absorption of inorganic mercury can best be assessed through measurement of the mercury content of whole blood. In an international study, the average concentration of mercury in the blood of persons without occupational or unusual exposure to mercury was found by atomic absorption spectrophotometry to be 5 ng per gram (0.5 μg per dl); 95 percent of values were below 30 ng per gram (3μg per dl).[5]

A diagnosis of organic (ethyl or methyl) mercury absorption or intoxication is based primarily on a history of exposure plus finding the classic signs on physical examination. In acute exposure to organic mercurials, a high degree of correlation has been found between average daily exposure and the total blood mercury concentration, as determined by atomic absorption spectrophotometry.[65]

Determination of the mercury content in hair is an unreliable diagnostic index of mercury absorption or toxicity.[5] Diagnostic chelation is of unproved efficacy and safety as a technique for evaluating increased absorption of mercury.

Arsenic

Sources of Exposure

Arsenic exists in two chemical forms—trivalent (+3) and pentavalent (+5). In general, the trivalent form is the more highly toxic.

Human exposure to arsenic occurs mainly through ingestion, particularly of seafood, or through inhalation of arsenic-containing airborne particulates.[6] Adults may be exposed to arsenic in the smelting of nonferrous ores, particularly copper.[6] More than 80 percent of the arsenic consumed industrially each year in the United States is used in the manufacture of pesticides, herbicides and other agricultural products.[66] Occupational exposures occur among chemical workers, pesticide formulators and pesticide applicators.[6] Arsenical salts, especially ammonia, copper and arsenic, and chromated copper arsenic, are widely used as antifungal wood preservatives. Increased absorption of arsenic has been found among carpenters working with treated woods, such as marine pier construction workers and also among workers engaged in arsenic application in wood processing plants.[67]

Community exposure to arsenic has been caused by airborne emissions from smelters—copper and gold smelters in particular.[44,68] Highest arsenic exposures have been found in children living very near to smelting plants, and exposures decrease geometrically with distance; near smelters, contaminated air, dust and soil appear to be the principal routes of exposure.[68]

Contaminated drinking water has also been found to be a source of chronic arsenic exposure.[69,70] Among a group of persons evaluated in Fairbanks, Alaska, the source of arsenic in their well water was found to be the native rock underlying the city; the gold-bearing strata in those rock formations were also rich in arsenic.[69] A similar explanation has been offered for the occurrence of high arsenic concentrations in well water in areas of Taiwan[70] and Chile.[71]

Toxicity

Acute arsenic poisoning almost always results from the ingestion of contaminated food or drink and is very frequently associated with homicidal or suicidal intent. The symptoms are those of profound gastrointestinal inflammation, sometimes with hemorrhage, and of cardiogenic shock.[6] Symptoms resemble those of cholera and may include difficulty in swallowing, abdominal pain, projectile vomiting, "rice-water" diarrhea, dehydration, a weak irregular pulse and a loss of blood pressure that is followed by the development of stupor, coma, convulsions and death. The fundamental lesion appears to be dilation and increased permeability of the small blood vessels in the gastrointestinal tract and elsewhere. Pathological examination shows extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine. The necrosis sometimes progresses to perforation of the gut wall. Fatty

degeneration of the liver and kidneys has been observed.[66]

Chronic arsenic poisoning is associated with lesions of the skin, nervous system, liver, cardiovascular system, hematopoietic system and respiratory tract.[66]

The dermatologic toxicity of chronic exposure to arsenic is characterized by eczematous dermatitis and by the appearance of hyperpigmented areas, warts (arsenical keratoses) and hyperkeratosis of the palms and soles. In an outbreak of arsenical dermatitis in a gold mining community in the Dakotas, 32 of 40 children (80 percent) who attended elementary school close to an arsenic-emitting ore processing plant were found to have arsenical dermatitis.[72]

Chronic arsenic exposure is associated with the occurrence of three types of skin cancer: squamous cell carcinoma, basal cell carcinoma and Bowen's disease; those lesions are frequently multiple in origin and develop primarily from arsenical keratoses.[66] The incidence of skin cancer in persons exposed to arsenic is related directly to their cumulative arsenic dose.

The principal neurologic abnormality associated with arsenic exposure is sensory neuropathy.[73]

In the liver, chronic exposure to arsenic has been associated with cirrhosis.[66] Chronic arsenic exposure has also been associated with angiosarcoma of the liver.[74]

Peripheral vascular disease has been observed among persons in Chile[71] and Taiwan[70] who had had chronic exposure to arsenic in drinking water. Early symptoms included acrocyanosis and Raynaud's phenomenon. Those changes were associated with hyperpigmentation and hyperkeratosis. They progressed in severe cases to frank gangrene of the extremities ("blackfoot disease"), associated with endarteritis obliterans. The prevalence and severity of blackfoot disease appeared to be related to the cumulative dose of ingested arsenic.

In the red blood cells, chronic exposure to arsenic has been associated with disturbed erythropoiesis, and megaloblastic formation has been noted.[66] These changes appear to reflect the inhibitory effects of arsenic on cellular respiration.

Arsenic is a potent irritant of the respiratory tract. In adults with chronic occupational exposure to arsenic, inflammatory and erosive lesions of the respiratory mucosa, including perforation of the nasal septum, have been noted.[66,72] Arsenic has also been shown to be responsible for the development of carcinoma of the lungs and bronchi.[66] Among 8,047 copper smelter workers exposed to arsenical dust in Anaconda, Montana, a threefold increase in the death rate from respiratory cancer was found over statewide rates.[75] Further, there was a systematic gradient in lung cancer mortality according to the duration and intensity of arsenic exposure; in the subgroup of workers with the heaviest and longest (more than 15 years) exposure, excess mortality from lung cancer was found to be increased eightfold over expected rates. Likewise, a study of 1,393 pesticide workers in Baltimore found mortality from lung cancer in all workers exposed to arsenic significantly higher than that in all Baltimore city workers.[76] Using a standardized mortality ratio of 100 to indicate that the number of deaths from a particular cause in a population equals the number expected from that cause (on the basis of age, sex and race) and ratios above 100 to indicate increased mortality, a positive dose-response relationship was noted in that study between lung cancer mortality and the duration of arsenic exposure. Mortality ratios ranged from less than 100 in workers exposed for less than one year to 2,750 (2 observed versus 0.1 expected) in workers heavily exposed for 25 or more years.

Evaluation and Diagnosis

Clinical evaluation of a person suspected of having been exposed to arsenic must take cognizance of the fact that arsenic has a biological half-life of only about ten hours; in primates, excretion of a single injected dose of arsenic is virtually complete within six days.[66] Arsenic is mainly excreted via the urine.

Human absorption of arsenic has been assessed through measurement of the total arsenic concentrations of blood, hair and urine.[69] Because of the short half-life of arsenic in blood,[66] the blood arsenic determination has been found to be of little practical value.[77] Also, given the short half-life of arsenic in the human body, provocative chelation is of little value as a diagnostic technique.

The determination of arsenic in hair is a semiquantitative indicator of past exposure to arsenic. In a nationwide survey of children living near primary smelters in the United States, the mean hair arsenic concentration in 972 children from 11 towns with copper smelters was found to be 2.60 μg per gram; the highest concentration (19.88 μg per gram) was found in Anaconda, Montana, the most heavily polluted town in the study.[44] By contrast, the mean hair arsenic content in 160 children from three towns without smelters was 0.09 μg per gram ($t=9.72$, $P<0.01$). The major drawback to the determination of arsenic in hair is that it does not distinguish systemically absorbed from externally deposited arsenic. Thus the intrinsic arsenic content of hair can be modified by bathing in arsenic-contaminated water, by contamination with arsenic excreted in sweat or by exposure to airborne arsenic. For those reasons, a diagnosis of arsenic absorption or toxicity cannot be based on an unsupported determination of hair arsenic content.

The urine arsenic concentration appears to be the best indicator of current or of recent (one to three days) past exposure to arsenic.[69] However, it is very important, given the short biological half-life of arsenic, to consider the timing of the collection of samples in assessing the biological significance of the arsenic concentration in urine.

Although the range of values considered "normal" in previous studies of urine arsenic concentration has varied, due primarily to differences in laboratory methods, most urine arsenic concentrations in unexposed populations have been found to be below 50 μg per liter.[66] Three studies[78-80] reported mean urinary arsenic concentrations in allegedly unexposed persons of 80, 85 and 130 μg per liter; however, in each of

TABLE —*Percent of Children Ages Six Months to Five Years With Blood Lead Levels of 30 μg/dl or More**
United States—1976-1980

	Race		
	White	*Black*	*All Races*
Both sexes	2.0	12.2	3.9
Boys	2.1	13.5	4.3
Girls	1.8	10.9	3.5

*From Annest & Roberts.[81]

those studies, persons in the control groups either worked in proximity to arsenic-contaminated areas or had previous occupational exposure to arsenic.[66]

Discussion

Toxic metals—lead, cadmium, mercury and arsenic—are ubiquitous environmental contaminants in an industrialized society. Although all of these metals are natural constituents of the earth's crust, their distribution has been radically altered by human activity, and they are now dispersed widely in air, food, soil and water.[3-6]

Absorption of these metals has become the norm rather than the exception among residents of the United States, and the margin of safety between present-day background levels and the levels associated with toxicity has become vanishingly small.

The extent of the problem of toxic metal exposure among residents of the United States is well illustrated by recently developed data from the national Health and Nutrition Evaluation Survey (HANES-II); HANES-II is based on a probability sample of the entire noninstitutionalized population of the United States. These data indicate that 3.9 percent of all United States children between the ages of six months and five years examined from 1976 to 1980 had blood lead levels of 30 μg per dl or more. With projection of that finding to the entire population of the United States, it may be estimated that 675,000 young children have elevated blood lead levels. There was, in addition, a pronounced racial discrepancy in the HANES-II data. While only 2.0 percent of white children had elevated blood lead levels, the prevalence in black children was 12.2 percent (Table 2), and among black children residing in the central core areas of large cities and in families with an annual income of less than $6,000, the prevalence was 18.6 percent. Given recent evidence that blood lead levels above 30 μg per dl in young children are associated with the development of irreversible intellectual and behavioral deficits,[34-39] the HANES-II data have profoundly disturbing implications not only for the future health of the affected children, but also for the integrity of the whole fabric of urban society.

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Ionizing Radiation and Its Risks

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Penetrating ionizing radiation fairly uniformly puts all exposed molecules and cells at approximately equal risk for deleterious consequences. Thus, the original deposition of radiation energy (that is, the dose) is unaltered by metabolic characteristics of cells and tissue, unlike the situation for chemical agents. Intensely ionizing radiations, such as neutrons and alpha particles, are up to ten times more damaging than sparsely ionizing sources such as x-rays or gamma rays for equivalent doses. Furthermore, repair in cells and tissues can ameliorate the consequences of radiation doses delivered at lower rates by up to a factor of ten compared with comparable doses acutely delivered, especially for somatic (carcinogenic) and genetic effects from x- and gamma-irradiation exposure. Studies on irradiated laboratory animals or on people following occupational, medical or accidental exposures point to an average lifetime fatal cancer risk of about 1×10^{-4} per rem of dose (100 per 10^6 person-rem). Leukemia and lung, breast and thyroid cancer seem more likely than other types of cancer to be produced by radiation. Radiation exposures from natural sources (cosmic rays and terrestrial radioactivity) of about 0.1 rem per year yield a lifetime cancer risk about 0.1 percent of the normally occurring 20 percent risk of cancer death. An increase of about 1 percent per rem in fatal cancer risk, or 200 rem to double the "background" risk rate, is compared with an estimate of about 100 rem to double the genetic risk. Newer data suggest that the risks for low-level radiation are lower than risks estimated from data from high exposures and that the present 5 rem per year limit for workers is adequate.

In the 87 years since the discovery of radiation and radioactivity, considerable information has become available concerning the characterization and quantification of radiation and its interaction with matter. More is probably known about the consequences of exposure to ionizing radiation than any other environmental or occupational hazard. Paradoxically, the increase in knowledge about the consequences of radiation exposure has increased its ranking as an issue of serious concern to society.

This brief overview will attempt to highlight some of the basic radiobiologic concerns that apply to the assessment of population and occupational exposures. It includes some discussion of the ways in which radiation risk can be quantified and assessed, and some areas of future concern.

The Nature and Measurement of Ionizing Radiation

The unique electrical nature of ionizing radiation renders it particularly amenable to easy detection and quantification. Regardless of the source, the absorption of ionizing radiation by matter is accompanied by the creation of ion pairs—that is, the physical disruption of neutral atoms caused by the dislodging of the target atom's orbital electron. The dislodged electron and the residual electron-deficient atom constitute an ion pair, and the process is known as ionization. This process can occur when electromagnetic or particulate radiation is absorbed in any target.

The kinds of exposures of principal concern to society are primarily from x-irradiation, gamma-irradiation and beta particle irradiation. These three types of

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ABBREVIATIONS USED IN TEXT

LET = linear energy transfer
RBE = relative biologic effectiveness

ionizing radiation all emit low linear energy transfer (LET) radiations, meaning that they have in common a characteristically sparse path of ion pair generation. Thus as radiation penetrates matter, it creates ion pairs with relatively large distances between them. Frequently these ion pairs appear in clusters. By contrast, high-LET radiation is characterized by relatively short range, very intense, closely patched ion pairs.[1]

The number of ion pairs absorbed within a volume of tissue constitutes the absorbed radiation dose and we quantify this absorption of electrical energy in terms of rads (radiation-absorbed dose). The absorption of 100 ergs of ionizing radiation in 1 gram of matter has a value equal to 1 rad. A new System Internationale (SI) nomenclature for radiation units has been adopted, and the term rad is now being replaced by an absorbed dose unit called the gray (Gy). One rad equals 0.01 Gy (specifically, 1 Gy = 1 joule/kilogram). The rad is a physical radiation absorbed dose unit which, when multiplied by a relative biologic effectiveness factor (RBE), permits one to account for the different biological effectiveness of radiations of different LET. The product of RBE times rads equals rem (rad equivalent in man or mammal). The SI replacement for the rem is the sievert (Sv), and 1 rem equals 0.01 Sv.

For purposes of continuity and convenience, rads or rems will be used in this discussion. Since the radiation discussed to the greatest extent is entirely of low-LET quality with an RBE value of unity, we can, in this context, use rads and rems interchangeably when considering x-, gamma- and beta-irradiation.[1]

Assessing radiation hazards requires knowledge not only of the essential characteristics of the quality of radiation absorbed by target tissues but also its distribution in space and time. As with exposures to many other substances, it has been observed in radiation research that as the doses absorbed by individuals increase, the magnitude and consequences of the exposure also increase. The rate with which a given dose of radiation is absorbed frequently plays a significant role in the manifestation of radiation effects.[2]

Some perspective on the magnitude of radiation doses might best begin with consideration of the annual background radiation dose to which all of us are exposed. This background radiation exposure is the result of cosmic radiation, of natural radioactivity from the earth's mantle beneath us and of the small amount of natural radioactivity that is present in all living tissues. The natural background radiation dose rate in the United States generally averages approximately 0.1 rem annually.[3] It can increase by about a factor of two in certain parts of the country where underlying terrestrial radioactivity might be slightly higher due to different geologic formations, and where, at high altitudes, the thinner atmosphere permits a slightly higher flux of cosmic radiation. For example, the annual background rate in California is approximately 0.1 rem per year, but in Denver, Colorado, it is about 0.2 rem per year. There are parts of France where the natural background rate is 0.5 rem per year, and in certain locales in Brazil and India it may be as high as 1 rem per year. It is evident that on this planet there is no such thing as a radiation-free environment.

It is realistic to assume over the course of our lifetimes we each accumulate radiation doses from background exposures of between 5 and 10 rem at exceedingly low rates. Although present estimates vary somewhat, if in addition one were to average all of the radiation exposures from the healing arts, consumer products and all other man-made sources, our average absorbed dose rate would double. Therefore, a typical American would receive approximately 0.2 rem per year, half of it natural and half of it man-made.[4]

There is no direct evidence to support any medical consequences from exposures to background radiation. Only when the radiation dose is greatly increased are the consequences measurable.[1,4]

Basic Interaction of Radiation with Biologic Targets

Ionizing radiation produces its effects by either directly ionizing and disrupting a molecule of critical importance to the cell (usually in the cell nucleus) or through the production of highly reactive free radicals (usually of water). These direct and indirect effects produce the initial lesion which may be amplified to produce radiation effects. Nonionizing forms of radiation can cause resonance or excitation of impacted atoms, but only ionizing radiation produces ion pairs.[5] Ionization has serious consequences in certain cellular structures. Many theories and much research address the sequence of amplifying steps from the initial atomic reaction following absorption of ionizing radiation to the manifestation of a clinical entity such as the initiation of a cancer or the creation of a genetic defect. The serious occupational health problems resulting from ionizing radiation stem from the killing of cells consequent to large doses of radiation, or from nonrepaired injuries in the form of molecular lesions in cells, primarily within the nucleus, that survive the radiation.

Cell and Tissue Radiosensitivity

The results of low LET radiation exposures of single cell preparations in vitro show that cell survival and reproductive capacity can be diminished by relatively high radiation doses.[5] Laboratory studies of human, animal and plant cells have shown that exceedingly small radiation doses given at very low dose rates do not necessarily produce an effect that is linearly proportional to the radiation dose.[6] In the lower dose domain, the data are consistent with the assumption that some of the initiating molecular events after the absorption of radiation doses are repaired, or "recovered," to some extent. To the extent that any repair occurs within these cells, and that this repair efficiency is dose related, the dose response will likely not be strictly proportional over the full range of tested radi-

ation exposures. As an example, when the radiation dose is quite low, as from the slow decay of a deposited long-lived radioactive element, a long time may be required and a substantial dose may be necessary before low-LET radiation-induced cancer can be found. At higher doses, radiation-induced cancer is likely to appear sooner.[8]

Different cells and tissues appear not to be quantitatively similar in their response to radiation exposure. About 80 years ago, Bergonie and Tribondeau observed that the sensitivity of cells to radiation seemed to be greatest in those cells that were most primitive, that divided most frequently and had the shortest interval between divisions. Cells of reproductive organs, cells lining the intestinal tract and the primordial cells of the bone marrow have these characteristics. Muscle and neuron cells are uniquely radioresistant, highly complex and nonmitotic.[9] As an aside, it is an interesting observation that cells in tissues that divide most rapidly do not necessarily correlate with potential radiation-induced cancer risk.

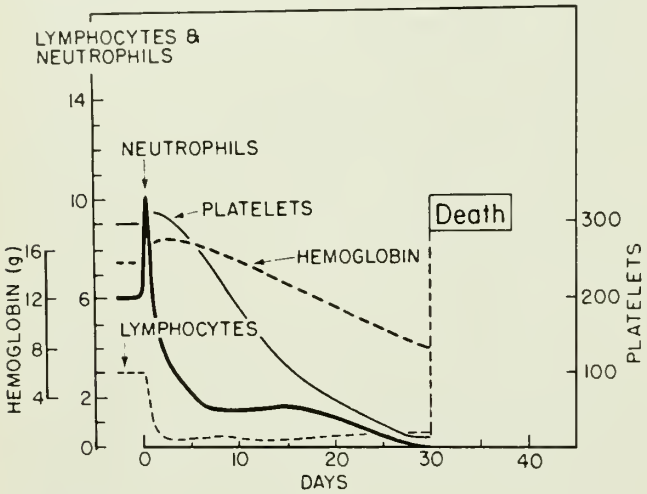


Figure 1.—Typical hematological response of human beings to total-body radiation dose of 450 rads. Lymphocyte, neutrophil and platelet values should be multiplied by 1,000. Hemoglobin values are in grams per dl. (Reproduced with permission from Andrews GA: Radiation accidents and their management. Radiat Res 1967; 7(Suppl):390.)

TABLE 1.—*Acute Effects of Whole Body Irradiation*

REM	
5-20	Possible late effect; possible chromosomal aberrations
20-100	Temporary reduction in leukocytes
100-200	"Mild radiation sickness"; vomiting/diarrhea/tiredness in a few hours Reduction in infection resistance Possible bone growth retardation in children
200-300	"Serious radiation sickness"; bone marrow syndrome; hemorrhage; $LD_{10\text{-}35}/_{30}$*
300-400	"Serious radiation sickness"; marrow/intestine destruction; $LD_{50\text{-}70}/_{30}$
400-1,000	Acute illness, early deaths $LD_{60\text{-}95}/_{30}$
1,000-5,000	Acute illness, early deaths in days; intestinal syndrome $LD_{100}/_{10}$
5,000+	Acute illness; death, early deaths in hours to days; central nervous syndrome $LD_{100}/_{2}$
Also	
50+	in men yields temporary sterility (100 rem+ =1 year duration)
300+	in women yields permant sterility

REM=rad equivalent in man or mammal; LD=lethal dose.

*Lethal dose to percentage of the population in number of days (for example, $LD_{10\text{-}35}/_{30}$=lethal dose in 10 percent to 35 percent of the population in 30 days).

Acute, Latent and Genetic Radiation Effects

If uniform radiation is absorbed by the body, a spectrum of effects is seen, each related in time and extent to the magnitude of radiation dose. Figure 1 illustrates a temporal sequence of changes in blood sampled from a person receiving a nearly lethal dose of radiation.[9] Note that the different cell types respond differently to the radiation exposure and that there are cell populations, in this case the bone marrow, that show some recovery towards the end of the sequence.

Identification of acute radiation effects can be summarized as shown in Table 1. It should be noted that if a hypothetical population were to receive a large exposure to radiation, and the population was sufficiently small, it is possible for medical intervention to ameliorate the severe consequences. It is a radiobiologic fact of life, however, that radiation-induced lesions and their consequences at high doses are to a very large extent nonreversible.[10] Large total-body doses of radiation impact most severely on the regenerative cells of the intestinal epithelium, on the regenerative cells of the bone marrow and on the microvascular system's endothelial cells. As a consequence, soon after irradiation a number of effects evolve in which phagocytic function is impaired, in which electrolyte containment within the body is compromised, and in which gastrointestinal integrity due to massive hemorrhage and cell depletion permits bacterial entry into the body from the gastrointestinal contents. The resulting loss of hematopoietic defenses, vascular integrity and electrolyte imbalance at radiation doses in excess of 300 to 400 rads is likely to be considered lethal.[10] Therapy in the form of antibiotic attack on bacterial infection, cell transfusion and even in some instances bone marrow transplantation has some moderate effectiveness. However, the microanatomic disruption of the body's defenses is not easily repaired by external sources and at best therapy constitutes a holding action until the surviving cells in the body can repair the initial damage. Furthermore, despite a massive research investment over the past three decades, there have been no successful preventive medications developed that could act as a competing target for the effects of ionizing radiation, and thereby minimize its impact.[5]

Early in the evolution of radiobiologic research, effects of radiation at doses lower than those needed for acute, immediate effects were frequently quantified in terms of life-shortening or acceleration of aging.[1] We now know that this to a very large extent appears to be another means of quantifying an increase in the acceleration of cancer risk statistics in populations exposed

to small to intermediate levels of radiation, and not to some unique change in physiology.

If radiation is protracted, its consequences are usually less severe than when the same radiation dose is delivered acutely.[7] For example, in a study on beagle dogs carried out at our laboratory some three decades ago, it was noted that when a dose of 300 rads of radiation was absorbed by dogs, the animals with the greatest interval between exposure fractions and the smallest radiation dose per fraction had decreased life-shortening or a lower cancer rate than animals receiving the same total dose in shorter intervals, or larger fractions.[11] The magnitude of this dose-rate amelioration factor was approximately a factor of 3 at its greatest (that is, a given dose via protracted radiation was a third as carcinogenic as the same dose given acutely). Another study now nearing completion in our laboratory on the effects of strontium 90, a low-LET beta-particle-emitting radionuclide that concentrates in the skeleton, shows that bone cancer is induced only when the radiation dose rates exceeded approximately 1 rad (or rem) per day, and then only after several years of exposure (that is, several hundred rems of dose).[12] A 1,500-fold range of doses was tested from about 7 millirads to 15,000 millirads per day, showing at the higher levels a full range of myeloproliferative disorders of marrow, as well as cancer of bone. The dose-response relationship does not appear to be a straight line, but is curvilinear. That is to say the curve is sigmoid or S-shaped, being very shallow at low doses and rising in a nonlinear fashion to a maximum level of effect at about 5 or more rads per day. Cumulative radiation doses associated with the radiation-induced cancers are above about 1,000 rads. The point to be made is that while cancer incidence is expected, it took rather large doses at low rates to be induced. Again, this appears to confirm that low dose rates are less efficient than high dose rates for the same total dose regarding the risk for cancer induction.

Recently the National Council on Radiation Protection and Measurements has cited tumorigenesis data on some 12 different studies in laboratory animals covering doses ranging up to 200 or 300 rem.[7] These all show that low-dose rate radiation is about two to ten times less carcinogenic for the same doses compared with radiation delivered at high rates. It is important to reiterate at this point that in the intermediate- and low-dose range, the principal, if not sole, radiation effect in the exposed population is the somatic risk increase for cancer. An increase in this risk in an exposed population can cause shortening of the lifespan.

Today the challenge to scientists, especially to epidemiologists and biophysicists, is the methodology involved in the computation of accurate risk estimates. Of considerable complexity, this health risk estimation is always done in a manner complicated by the way in which the normal cancer statistics of the population at risk are to be handled. Approximately 1,700 people per million each year die of cancer from all causes.[10] It is known that this disease is predominately one of old age, as shown in Figure 2, in which most types of cancer have an almost exponential increase with age.[4] It is on this natural history of cancer incidence and mortality

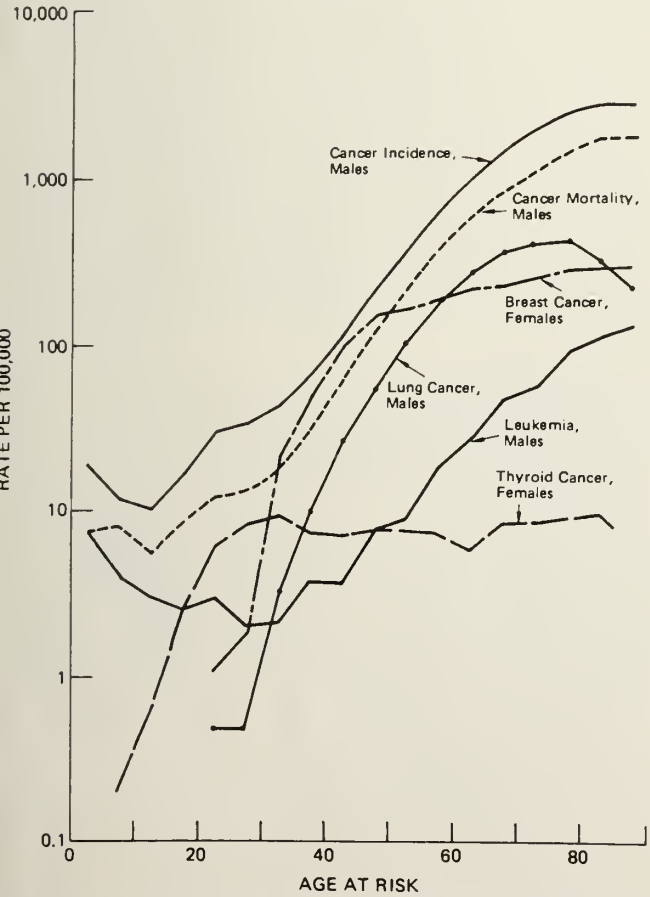
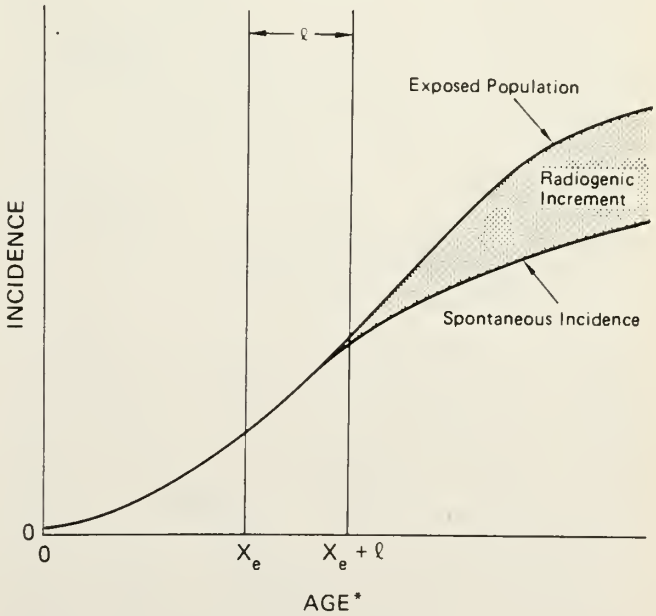


Figure 2.—Age specific cancer mortality rates (from National Academy of Sciences[4]).



*X_e is age at exposure, ℓ is the minimal latent period.

Figure 3.—Radiation cancer incidence. Following exposure (X_e) a minimal latent period (ℓ) precedes the radiogenic cancer increment added to the spontaneous incidence in the exposed population (from National Academy of Sciences[4]).

that our calculations of additional risk from radiation exposure are built.

The risk (Figure 3) associated with each incremental increase in radiation dose can be described in terms of a time following irradiation in which no medical evidence is seen, and is frequently referred to as the latent period.[4] For most solid tumors this is of the order of 5 to 15 years. For leukemia, it is much less, probably two to five years. In a population of exposed persons, this latent period will be followed by an increase in risk. This plateau or height is proportionally related to the intrinsic radiosensitivity of the tissue in question, and whose duration of risk may be short in the case of leukemia, or quite long in the case of solid tumors. Three hypothetical organs and their radiation risks are shown in Figure 4, which is constructed to illustrate this point.

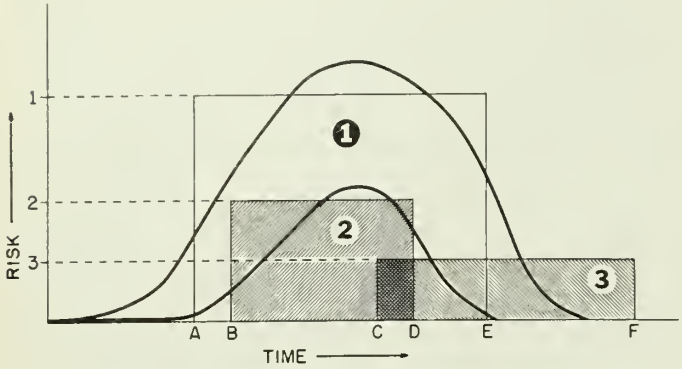
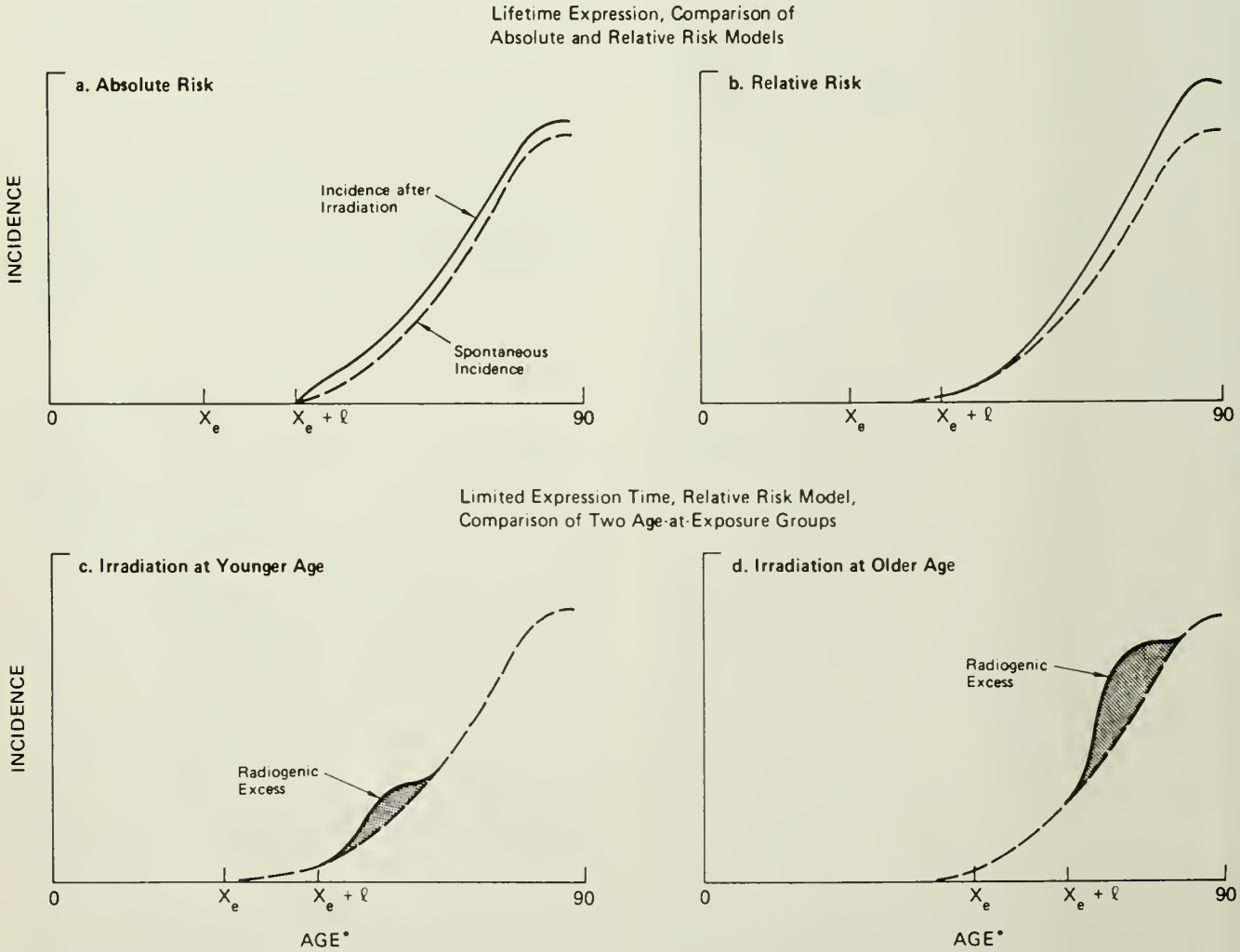


Figure 4.—Latency and sensitivity. These three hypothetical organs each exhibit unique latencies, magnitude of risks and duration of "risk plateau." The data in boxes 1 and 2 are derived from the incidence rate curves shown.

The models utilized to quantify radiation cancer risk are generally summarized in terms of either an absolute or relative risk model for young or old persons. In Figure 5 the National Academy of Sciences recent BEIR (Committee on Biological Effects of Ionizing Radiation) report illustrates the differences between these models.[4] The relative model assumes a radiogenic cancer risk in proportion to the natural prevalence of the disease in that organ for the given age, whereas an absolute model implies a fixed increment of risk for doses that is independent of age or the "normal" risk for cancer in the organ.



*X_e is age at exposure, ℓ is the minimal latent period.

Figure 5.—Several models of radiation risk (from National Academy of Sciences[4]).

The most conservative approach to radiation risk assessment is to assume a no-threshold linear model, a straight line whose slope predicts that risk increases as dose increases, the assumption here being that each and every incremental increase in dose is associated with corresponding equal increment in risk. Recent radiobiologic studies, particularly those in animals and cells in culture, suggest that the linear model overstates radiation risk at low levels.[1,7,13,14] In Figure 6, I have attempted to summarize this phenomenon. The small low-dose box containing a question mark is the region of primary concern to occupational medicine and population regulatory interests in that the extrapolation to it from the high-dose data base down to the exceedingly low dose depends upon the model used. The linear model will give a higher predicted risk than the sigmoid S-shaped model or the dose squared or quadratic model. High-dose rate radiation in particular, and especially that from high-LET emitters such as alpha particles, generally follows a more linear model than does the more conventional low-LET radiation.

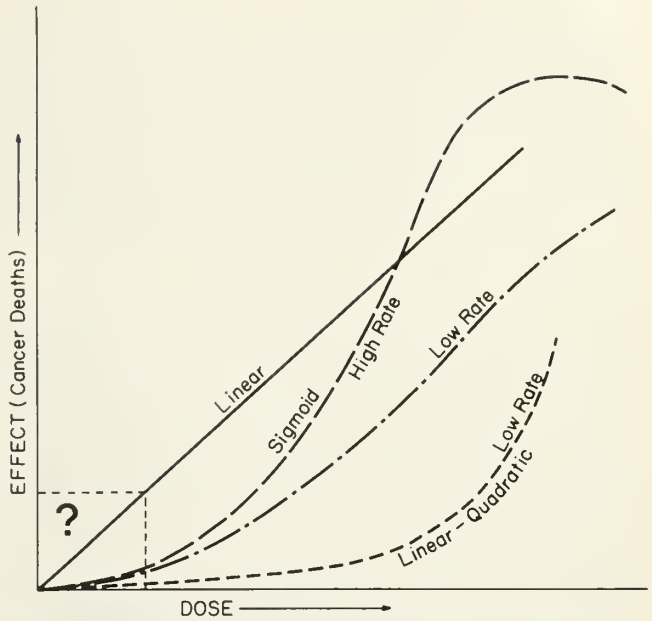


Figure 6.—Radiation risk models. Data fit to the higher dose domain can greatly influence the size of the effect (or risk) prediction in the very low dose range (shown by ?).

Genetic effects of radiation have been known for more than 50 years stemming from the pioneering research on effects of ionizing radiation on *Drosophila*.[1] One very significant finding associated with the early studies was the linearity of the response for the particular endpoints measured. Linearity, however, may not be the case for the mammalian genetic system. Much, if not almost all, of our information regarding the genetic consequences of ionizing radiation stems from important research at Oak Ridge on mice, the "Megamouse Study," in which approximately a threefold dose rate effectiveness factor was noted for effects in the alleles tested in mice when dose rates were low relative to the yield at the same total dose delivered at higher rates.[1] Ongoing studies of the survivors of the bombings at Hiroshima and Nagasaki have not found genetic effects in the offspring, although much of our knowledge about radiation-induced cancer in humans has been derived from the follow-up of those irradiated populations.[4]

Effects of Radiation on the Embryo and Fetus

If, as Bergonie and Tribondeau predicted, primitive rapidly dividing cells are the most sensitive, one would expect the developing mammal in utero to be particularly vulnerable to ionizing radiation. Much of our observation on this subject derives from studies in rodents in which it was observed that LD_{50} doses delivered to the embryo invariably resulted in lethality, whereas the same radiation dose delivered to the fetus would induce a spectrum of deformities and anomalies most likely associated with the anlage undergoing differentiation at the time of radiation. It is not known whether embryo death and abortion occurred significantly in pregnant women after the Hiroshima and Nagasaki bombings, but studies on the persons who were at fetal age at time of the bombing have shown only a possibly slight decrease in cranial circumference at birth for those irradiated in the third trimester.[1] The risk for fetal injury based on the mouse model is sufficiently sensitive so as to suggest that a fetus receiving in excess of about 10 rem has a high likelihood of being born with a serious defect.[4] In some instances, abortion is recommended following doses in excess of 10 rem. Women during their fertile years therefore have the added consideration of potential embryonic or fetal exposure associated with radiation-related occupations.

Occupational Exposures

The earliest occupational exposures were among the pioneers in radiology—Röntgen, Becquerel, Curie and the like—who at the time of their remarkable discoveries had no knowledge of the potential health implications of abusing this interesting but difficult to detect form of energy. The early literature is replete with descriptions of lost limbs, blindness, skin lesions and induction of neoplasia. Cancer in early radiologists was particularly common, although it is reassuring to note that the radiology specialty today enjoys about the same cancer mortality statistics as do other medical specialties that do not deal with ionizing radiation.[4]

Early in the century, clock and watch dials were luminized by manually applying to their faces a radium-containing paint.[14] This application with small brushes, usually done by young women, frequently involved "tipping" the brushes with the lips to make the numerals clear and precise. The brush tipping by mouth resulted in the ingestion of small quantities of radium-containing paint. The radium, an alpha-emitting long-lived divalent bone-seeking cationic radionuclide, induced skeletal lesions, including bone cancer and pathologic fractures. Because of its long radioactive and biologic half-life, investigators were provided the opportunity for retrospective dosimetric estimations in people. When the hazards of radium poisoning were recognized and tipping of brushes was prohibited, those

subsequently in that industry have today shown none of these rare lesions. Follow-up and measurement of hundreds of survivors of this industry, as well as some unusual medical detective work, have developed an estimation of risk for this high-LET alpha-emitting radionuclide that strangely appeared not to be linear with cumulative radiation dose, and may even indicate that at low-dose rates the risk, as in low-LET radiation, is curvilinear or that osteoid tissue has some different sort of response.[15]

More recently, epidemiological studies of workers at the atomic plants at Hanford, Washington, and those at Portsmouth Naval Shipyard in New Hampshire who were involved in the construction and maintenance of nuclear submarines, and of civilians and military participants in above-ground weapons tests are being closely studied to determine if evidence exists to suggest an increased cancer risk from the work environment. Some preliminary reports have been issued but the final assessment remains to be completed.[16] In each of these groups the major obstacle to the epidemiologic follow-up is the fact that a relatively small number of persons are involved. The radiation risk at low levels is low and in most cases ill defined, and the appropriate control cohort frequently has to contend with problems such as the "healthy worker" syndome, in which the exposed persons appear to outlive their unexposed comparison group. The range of radiation doses involved and the range of cancer risks implied do not at this time indicate that our present understanding and quantification of radiation risks are grossly misplaced.[4]

Radiation Risk and Regulations

Values from the available literature on radiation risk assessment suggest that a central estimate for fatal cancer in an exposed individual is about 1×10^{-4} per absorbed rem.[1,4] This is another way of saying that if a million persons were each to receive a rem, approximately 100 additional cancer cases might be added to the 170,000 that would normally be expected in a life-table analysis of such a population size. Risk estimate numbers that ranged widely earlier, now appear to be converging and approximate a value not higher than 200 and probably less than 50. The higher values depend upon the use of a relative risk model. The lower values assume constant radiation sensitivity throughout lifespan and are based on an absolute model. Both the National Academy of Sciences[4] and the United Nations[1] have published numbers that are quite similar. The same data base is used of course by both groups and in some instances the same experts are doing the analysis.

The case for genetic risks is not quite so clear in view of the absence of confirmatory evidence in humans. However, the best current estimate is that 100 rem delivered to a population would probably double the incidence of genetic defects above that which is normally expected. Another way of summarizing this value is to estimate it in terms of about 60 serious genetic defects per million live births per rem. About a fourth of these would appear in the very first generation.[4]

Radiation regulations over the years have consistently declined from numbers that initially were stated in terms of radiation exposure limits per day to our current standards in this country as posted in the code of Federal Regulations 10 CFR 20 that workers shall not receive in excess of 5 rem per year, or 3 rem per quarter (sometimes interpreted as 12 rem per year). Somewhat larger annual doses are permitted for the limbs. Regulations also state that the general population shall not receive in excess of a tenth of the occupational level.[3] The reasoning here is that those people working with radiation are generally involved in a monitored environment in which exposures are known. This may not be true in the general population.

More recently, radiation protection philosophy has introduced the concept of ALARA, "as low as reasonably achievable." Whatever the dose limit may be in a stated regulation, employers are now required to show that the ionizing radiation exposure potential to workers is to be maintained at levels that are as low as reasonably achievable. This introduces the concept of a collective dose risk problem. For example, if an industrial process entailed a significant radiation exposure potential, is it better to have that radiation absorbed in relatively larger doses by few persons, or to spread the same radiation dose over many people, each receiving smaller doses? In the spirit of ALARA, the latter would be preferable. However, when the same job or work is spread out over a greater number of persons it is not likely that a commensurate increase in efficiency will occur and in general experience has shown that the *total* amount of radiation absorbed by the worker population assigned to a task increases as the average or unit or individual radiation dose decreases. The risk one would calculate, therefore, is highly dependent on whether one uses a curvilinear or a linear model for this low-dose domain. A linear model would say that spreading the dose out increases the risk. The curvilinear model says the opposite. Time will show which, if either, is correct.

Radiation Issues in Society

The radiation issue is probably one of the most widely discussed in the professional and lay press. Some of the issues discussed above that have yet to be resolved involve the precise quantification of the dose-response relationship. Is it linear or is it something else? If so, how can we prove it? Buried in this particular issue is another issue regarding the purported supersensitivity of certain small subsets of the population, for example, those who may be considered to be at high risk for cancer or genetic problems, or some other medical condition. For these persons should the standards be lower?

A second issue of considerable importance is the potential synergism between the physical risk associated with ionizing radiation and the potential environmental cancer risks from chemicals. If the same organs are at risk will small absorbed doses of both act synergistic-

ally, antagonistically or in an unrelated fashion? The literature on this particular point supports a variety of hypotheses, but in no way is the answer clear at this time.

An issue that goes beyond radiation biology relates to the problem of fertile women in the workplace. If the fetus and embryo are uniquely sensitive, then the standards relating to the fetus may be imposed on the woman; this provides the potential for discriminatory actions in order to protect the unborn.

Another issue relates to the quality of radiation. Over the past few decades, it has been conventional in the formulation of regulations and in the discussion of qualities of radiation to ascribe a constant factor, called a quality factor or a relative biologic effectiveness factor, to relate, for example, one type of LET radiation to another type of LET radiation. That the endpoints differ for different doses and rates and that the nature of the response curves for the two compared radiations appear not to be linear imply that a simple ratio is no longer applicable for risk estimation purposes. Instead a range of comparisons may be more appropriate.[8] An extreme example is in the case of comparison of high-LET alpha particles to low-LET x-rays at doses in which the x-ray effect approaches zero. When the denominator approaches zero the ratio approaches infinity; the inference would be that the high-LET radiation has some unique potency at low levels rather than that the comparison had almost no impact.

Lastly, what may appear to be more of a political issue is my observation that as information has been gleaned about the quantification of radiation risk, society appears less inclined to accept these values. This is not to imply that ignorance is bliss and that knowledge is a liability, but at times it is difficult to reconcile with the facts the difference between not having done the risk estimation and not liking what the risk estimation says once it has been done. In my opinion, radiation risk estimation represents a prototype for occupational hazards from other exposures. The scientific/societal interaction with these radiation risk estimates will likely set the precedent for many other agents whose potential occupational health implications we are just now learning to question.

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Diffuse Malignant Mesothelioma: A Review

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Diffuse malignant mesothelioma is a signal tumor of asbestos exposure. Mesothelioma incidence has been steadily rising during the past two decades, reflecting the increases in asbestos use during and following World War II. The onset of the disease follows exposure by 25 to 40 years. The dose-response relationship appears to be much lower than that for asbestosis or lung cancer—it is not known whether current levels of exposure will entail a risk for disease 30 years hence. There is no synergistic or additive interaction with smoking for this tumor. Current knowledge indicates that pleural plaques, per se, do not increase the risk for this tumor beyond that of the previous asbestos exposure alone. Durable fibers with high aspect ratios, especially amphiboles, are associated with experimental tumor induction. Treatment modalities including surgical procedures and chemotherapy with doxorubicin and 5-azacytidine offer prospects for palliation.

Diffuse malignant mesothelioma (DMM) has been referred to as a "signal tumor" because of its unique association with occupational or environmental exposure to asbestos.[1] This relationship was first noted over 35 years ago and has been chronicled in more than 175 scientific reports.[2-16] The association with asbestos has now become widely recognized as causal.

The latency period for DMM after the start of asbestos exposure is 25 to 40 years or more. A dramatic increase in the use of asbestos began during World War II and continued over the subsequent three decades; thus, during the 1980's and 1990's, physicians may encounter this tumor more frequently. In contrast to bronchogenic carcinoma, there is no interaction between cigarette smoking and asbestos exposure in the development of this tumor.

A physician suspecting a diagnosis of DMM should take an assiduously thorough occupational history. Most patients are men, reflecting an occupational exposure, but a fleeting or casual exposure in a shipyard, or exposure by working with asbestos in the arts, or by serving an apprenticeship to a lagger may be sufficient to initiate the disease. Contact with asbestos in the environment, such as living or playing near an asbestos factory or tailings dump, or growing up in the household of an asbestos worker who wears asbestos-covered workclothes home from work, may constitute sufficient exposure.

Incidence

The incidence of DMM can be determined from autopsy or pathologic studies, epidemiologic studies and population-based cancer registries. All three sources of data suggest that the incidence of this tumor has increased over the past two decades and that only part of this increase can be explained by a heightened awareness of the disease by physicians and by their improved diagnostic acumen.[17] Furthermore, the increase probably has not peaked because the tumor has such a long latency period. Incidence rates tend to parallel death rates, because patients seldom live longer than 12 to 18 months after diagnosis.

The annual incidence for adults varies between two and three cases per million for men and approximately 0.7 cases per million for women.[18] Theriault and Grand-Bois reported 2.3 to 2.8 cases per million a year in Quebec (where there are asbestos factories, mines and mills), while shipbuilding cities have higher rates, ranging from 5.6 to 8.9 cases in England to 21.4 cases per million a year in Trieste, Italy.[19-21] Autopsy rates have been lower; for example, 0.24 percent from 69,302 autopsies (165 mesotheliomas), representing six series from eight cities from 1950 to 1970.[22] Patients with mesothelioma may selectively be underrepresented in autopsy series, in part because the pathologic diagnosis is notoriously difficult. Reports from pathologists in Canada have shown a 2.5-fold increase of DMM in men in only a

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decade.[18] Population-based cancer registries have also documented an increase; for example, there has been a tenfold rise in incidence over three decades in cases recorded in the Connecticut Tumor Registry.[23]

Three fourths of the patients suffering from this disease are men, presumably reflecting occupational exposures. Eighty percent of the cases affect the pleura with the remainder predominantly located in the peritoneum. A greater proportion of peritoneal DMM has been reported in asbestos insulators, who may have had a heavy exposure in the distant past and presumably swallowed many fibers or had extensive translocation to the peritoneum. Also, more than 80 percent of cases occur during the sixth decade of life or later.

Association With Asbestos

In 1943 Wedler first associated DMM with asbestos exposure, and in 1947 the first report of mesothelioma occurring in the United States was published in the Case Records of the Massachusetts General Hospital.[24,25] Further case reports published in 1953 and 1954 described a pleural and peritoneal mesothelioma with parenchymal asbestosis.[26,27] Scant attention was paid to these case reports associating asbestos with mesothelioma until 1960 when Wagner and associates reported 33 cases of DMM; 32 of the patients had a history of known or potential previous asbestos exposure.[28]

Subsequent case series reports and cohort mortality studies have corroborated the epidemiologic association with exposure to asbestos.[1,29] Case-control studies have consistently found an asbestos exposure relationship with risk for DMM. Selikoff and colleagues have reported that 8 percent of 17,800 asbestos insulators in the United States and Canada whose cases were followed from January 1, 1967, to December 31, 1976, died from DMM.[30] A dose-response relationship has been shown with greater intensity and duration of exposure in an English asbestos factory.[31,32] Whitwell and co-workers extended these observations by determining the light-visible asbestos fiber content of a 1-gram specimen of dried lung using phase contrast microscopy.[33] They found 83 percent of 100 patients suffering from DMM had 100,000 fibers per gram, 80 percent of 100 lung cancer patients had 20,000 fibers per gram and 71 percent of 100 controls had 20,000 fibers per gram.

A history of asbestos exposure can be confirmed in most cases; however, persistence and skill are required in eliciting and interpreting an asbestos exposure. A physician should take a chronological occupational history, giving special consideration to jobs held and possible exposures 20 to 40 years earlier. Asbestos exposures that may cause mesothelioma are encountered in every stage of the production and use of asbestos. Exposures occur in the mining, milling and transportation of raw asbestos. Exposure occurs in asbestos factories in the manufacture of asbestos cement pipe, friction materials, textiles, roofing materials and other products. Construction workers are exposed to asbestos in a variety of occupations—including asbestos insulators, plumbers, welders and electricians. Workers in electrical power plants may be exposed. Many shipyard tradesmen were exposed as "innocent bystanders" while pipecoverers sawed, cut and fitted asbestos into place, or while laborers ripped out asbestos insulation during ship refitting. Asbestos insulation workers exposed in their trade in the past have the greatest relative risk for DMM.[34]

In a prospective study from South Africa, assiduous occupational histories have been obtained in DMM patients.[35] Asbestos exposure criteria included four months of constant exposure to an atmosphere of visible floating asbestos fibers, or four years in room contact with loose fiber not visible in the atmosphere, or three years' residence adjacent to an asbestos production facility. Of 70 consecutive cases of DMM, 69 met these criteria. The series has recently been extended to include more than 130 patients with similar results. Occupational histories are less reliable from family members or relatives of patients and least reliable when obtained from hospital records.[36,37]

A history of household contact with an asbestos worker and hobbies or avocations using asbestos in the home may even be important. During the 1940's and 1950's, when wives washed their husband's contaminated workclothes, they resuspended fibers in the air, possibly exposing the entire household. Anderson and associates reported four cases of DMM from household contact and reviewed 33 other cases where household exposure had been present.[38] A relative risk of ten versus matched, unexposed controls for this type of exposure has been reported utilizing a retrospective case-control technique.[39] Prolonged residence near a shipyard or factory, often 20 to 30 years before onset of the disease, has also been associated with DMM. In 1965 Newhouse reported an occupational or household contact in 40 of 76 cases of DMM versus 9 in matched controls. In addition, 11 of the patients versus 5 controls lived within half a mile of a factory.[40]

Pleural plaques or thickening (or both), despite a single case report, has not been shown to lead directly to DMM.[41] Even though several studies have shown an increased mortality from lung cancer and DMM among asbestos-exposed shipyard workers with pleural disease, the level of risk is still not clear.[42-44] In Finland, where pleural disease is common in the anthophyllite mining region, DMM has not been reported.[45,46]

Clinical Signs and Symptoms

The preeminent symptom of pleural DMM is chest pain; most often it is a persistent, gnawing pain in the involved side. Pleuritic pain is unusual but may occur when the tumor produces a spontaneous pneumothorax. Dyspnea on exertion and weight loss are frequent accompanying symptoms. The major sign is pleural effusion, which may be either serous or serosanguinous. The fluid has a tendency to reaccumulate rapidly following thoracentesis. Pleural effusion is usually the first sign of the tumor and may be present for several months before a diagnosis can be made. Dense pleural thickening is also common, without an effusion being demonstrated radiographically. Results

of blood chemistry studies usually are normal, but the serum lactic dehydrogenase level may be increased.[47] Malignant mesothelioma has also been reported to occur in the pericardium, atrioventricular node and tunica vaginalis testis.[48-51]

Advanced signs and symptoms of DMM include fever, syndrome of inappropriate antidiuretic hormone secretion, arthralgias (usually of fingers, wrists, ankles and shoulders), thrombocytosis and clubbing.[52] Other findings may include cough, hemoptysis, localized edema, Horner's syndrome, vocal cord paralysis, hoarseness, dysphagia and superior vena cava syndrome.[53] The disease advances insidiously with tumor extension involving contiguous structures (rib, lung, diaphragm); metastasis may occur via lymphatics or the bloodstream during later stages of disease. Although seldom manifested clinically, metastatic lesions are frequently found at autopsy. They may involve the contralateral lung, regional lymph nodes, liver, adrenal glands, bone, brain and spinal cord.[54,55] Primary carcinoma and DMM may be discovered simultaneously; it is possible that many of the tumor nodules on the pleura or peritoneum may have arisen de novo rather than from metastasis. Pleural mesotheliomas may spread to the peritoneum and vice versa. Because DMM is often difficult to diagnose by histologic examination, it is important to distinguish pleural metastatic lesions from primary tumors of the lung, gastrointestinal tract, pancreas and ovary with appropriate diagnostic tests.

Figure 1.—X-ray film of the chest showing right pleural effusion and diffuse malignant mesothelioma in a 63-year-old brickmaker who made bricks containing asbestos from 1942 to 1955.

Figure 2.—Computerized axial tomographic scan from the same patient as in Figure 1 illustrating tumor in the right thoracic cavity.

X-ray studies of the chest (Figure 1) usually reveal a large pleural effusion accompanied by a lobulated pleural density encasing the entire lung.[56,57] Pleural plaques may be noted enface, in profile along the lateral chest wall and atop the diaphragm. They are frequently calcified. Parenchymal asbestosis cannot always be identified on x-ray films, and is more noticeable in the uninvolved lung. Computerized axial tomography (Figure 2) may show the thickened tumor along the chest wall.[12]

Microscopic examination of the sputum rarely shows malignant cells, unless the tumor has invaded the lung parenchyma. Asbestos bodies are sometimes seen in the sputum or lung parenchyma, and in rare cases in the tumor.[58] Cytologic examination of pleural fluid is useful in a half to two thirds of the cases, depending on the experience of the cytologist; however, distinguishing DMM from metastatic adenocarcinoma or benign inflammatory conditions is often difficult. Roberts and Campbell successfully identified 8 of 14 and Butler and Berry 25 of 26 cases of DMM by the presence of malignant mesothelial cells in the pleural fluid.[59,60] Finding cell aggregates with a collagen core in the pleural fluid assists in differentiating DMM from metastatic carcinoma.[61] Electron microscopy of malignant and atypical mesothelial cells may also be useful.[62]

Malignant mesothelioma may concentrate gallium 67, and scanning with this radioisotope may prove useful in the future in differentiating malignant from benign pleural disease.[63] The scan may be useful in staging the disease at the onset of treatment and monitoring for recurrences during therapy.[64]

Examination of a pleural biopsy specimen is necessary for accurate diagnosis, even if cytologic findings are abnormal. Accurate diagnosis of DMM requires large biopsy specimens because there is considerable variability among areas of the same tumor, often with large amounts of intervening fibrous tissue. An open pleural biopsy is recommended, which can be combined with a procedure to remove tumor mass. Thoracoscopy with biopsy of pleural masses is an effective, specific technique that may supplant open biopsy, especially if the surgeon has experience with this procedure. DMM has been reported to grow into incisional sites, even needle biopsy tracks, causing considerable pain, but this is uncommon.

Pathologic Diagnosis

Primary neoplasms of the pleura were first recognized by Wagner in 1870, and Klemperer and Rabin popularized the term "mesothelioma" in 1932.[65,66] They also described two types of mesothelioma: the benign, solitary mesothelioma and DMM. The benign, solitary

type remains localized, although it may grow large and compress neighboring thoracic structures. It seldom has signs of malignancy and no association of this type of mesothelioma with asbestos exposure has been found to date.[67] The predominantly fibrous nature of the tumor has promoted the name "localized fibrous tumor of pleura"; it appears to arise from fibroblasts and other connective tissue elements in the areolar submesothelial cell layers of the pleura.[68] By contrast, DMM arises from either the pluripotential mesothelial cell or the primitive submesothelial mesenchymal cell, which retains the ability to form epithelial or connective tissue elements.

On gross examination, numerous tumor nodules may be noted, and in advanced cases the tumor bulk has a hard, woodlike consistency. On histologic examination variation among areas of the same tumor is characteristic.[69] In a series of 382 cases of DMM, 54.5 percent were epithelial, 21.5 percent sarcomatous and 25 percent mixed (biphasic).[70] Mesothelioma tumor boards have been formed in the United States, Canada, South Africa and Western Europe to assist in accurate pathologic diagnosis.[71]

The ultrastructure of mesotheliomas is composed of mesothelial cells joined by infrequent desmosomes. The cells are covered with irregular microvilli that may be seen within crypts in the cytoplasm. The cells have a prominent, dilated, rough endoplasmic reticulum containing basement-membrane-like material. Collagen formation by tumor cells may be prominent. The cells are embedded in a matrix of basement-membrane-like material containing fibrillar elements.[72-75]

Histochemical techniques may be valuable in confirming the diagnosis. Acid mucopolysaccharide (for example, hyaluronic acid) is detected in more than 75 percent of well-differentiated DMM, but is found less frequently in the more undifferentiated forms.[76-80] The Hale colloidal iron or alcian blue stain may show the presence of cytoplasmic vacuoles containing hyaluronic acid. Following hyaluronic acid digestion, the colloidal iron stain will be negative. The PAS and mucicarmine stains are negative for hyaluronic acid, but are positive for mucin in mucin-producing adenocarcinomas. Carcinoembryonic antigen is usually present in tumors of bronchial epithelial origin and absent in mesotheliomas.[81]

Therapy and Prognosis

Individual therapeutic modalities have had little or no success; therefore, the treatment of DMM is best approached by a combined regimen of pleurectomy, followed by radiation therapy, chemotherapy and possibly immunotherapy.[82-84] Chahinian and Holland have recently reviewed the available therapies.[85] Borow and associates reported a series of 72 cases from Somerville, New Jersey, site of a large asbestos factory.[86] The median survival was 15 months. One patient lived 2½ years, but none of the others survived more than 19 months.

Chahinian and co-workers prospectively evaluated 69 patients from 1974 to 1980, finding that several factors correlated with survival: patients whose tumors were in the pleura survived twice as long as those with peritoneal tumors; survival for patients with the epithelial type was longer than for those with biphasic or fibrosarcomatous types of tumors. Those younger than 65 years, those who respond well to chemotherapy and those who had had a previous surgical resection all survived longer.[87] The median survival was 12.1 months for all cases. Radical pleural resection resulted in 18 months median survival in 6 cases, and 7 of 28 patients with pleural mesothelioma responded to administration of doxorubicin and 5-azacytidine, achieving a median survival of 22.2 months from first treatment.

Immunotherapy may have a role in longer survival, because depressed T-cell function has been observed in some but not all patients.[88,89] In nine cases of DMM, the percentage and actual number of T-lymphocytes were reduced, and the response to the synthetic mitogen phytohemagglutinin was also impaired.[88] Using microcytotoxicity methods, Embleton and co-workers detected little or no tumor-directed cell-mediated immunity against cell cultures from pleural effusions of patients with malignant mesothelioma.[90] In a case report, a patient who had an intact immunological system as measured by lymphocyte surface markers and function values was alive seven years after diagnosis.[91]

Differences in Risk Based on Asbestos Fiber Type and Occupation

A gradation of DMM risk based upon type of asbestos fiber (crocidolite greater than amosite greater than chrysotile) has been claimed.[92,93] This variation may be due to physical properties of the fiber; for example, surface properties, aspect ratio, durability or its pulmonary deposition and retention. Timbrell and colleagues have suggested that the reason most cases of DMM in South Africa have come from the northwest Cape Province crocidolite fields is due to the thin fibers with high aspect ratios (length to width) that are found there.[94] Workers who manufactured gas masks from crocidolite during World War II have had a 16-percent mortality due to DMM, while Elmes found only one case among those who used chrysotile for gas mask manufacture.[95-98] Selikoff's group has reported an increased DMM mortality among workers in an asbestos factory using only amosite.[99] Exposure to tremolite in the whitewash or stucco of homes in Turkey has been associated with DMM.[100] DMM has only rarely been reported among Quebec asbestos miners and millers; for example, McDonald has found only 11 cases for a death rate of less than 0.3 percent.[18] The relative risk for DMM is greater in factories using chrysotile fiber than in chrysotile mines; and factories using both chrysotile and amphibole fibers have an even higher risk.[101] Some investigators have suggested a fiber-fiber synergistic action as the cause of DMM.[102] Fibrous erionite (a zeolite aluminum silicate) may interact with asbestos (tremolite, chrysotile) in natural deposits in Cappadocia, Turkey, to cause the high DMM rates found there.[103,104] The differences in mesothelioma occurrence

are much greater for different asbestos fiber types than for different types of work.

Tissue Analysis for Fiber

Both lung and pleural tissue specimens have recently been studied with a variety of techniques to isolate, quantitate and identify fibers. Lung specimens have contained a preponderance of amphiboles with little chrysotile found, even in known cases of mixed or predominantly chrysotile exposures.[18] Magnesium is leached from chrysotile, and chrysotile may either dissolve in tissue or be preferentially cleared from the lung.[105] Most fibers found in pulmonary tissue are less than 6 μm in length, and most chrysotile fibers are less than 2 μm long and 0.125 μm in diameter. Only a small proportion are long fibers, with amosite and crocidolite being predominant. The fate of fibers in the lung depends on their size, with the clearance of short, single fibers being much more rapid than that of long fibers in bundles.

Of great interest is the comparison of fiber types and lengths found in lung and parietal pleura. In 29 cases, Sebastien and co-workers isolated predominantly short chrysotile from the parietal pleura, whereas amphibole fibers were the predominant material (mean 56 percent) found in the lung.[106] However, this group did find short chrysotile fibers in the peripheral areas of the lung instead of the amphibole fibers found in central areas.[107] LeBouffant has also suggested a selective concentration of short (less than 5 μm) chrysotile in pleural tissue in contrast to the long amphibole fibers found in lung tissue from patients suffering from mesothelioma.[108]

When Jones and associates studied lung tissue from 86 confirmed cases of DMM, they found amosite and crocidolite to be about ten times more common than in controls.[109] Chrysotile was the same in both cases and controls, and in 30 cases there was no chrysotile. It would be interesting to study uninvolved parietal pleura from such a series for fibers. McDonald has corroborated these findings in 37 matched pairs of DMM and controls from North America.[18] Gylseth and colleagues did fiber counts in 15 cases of DMM, finding a range of 2 million to 490 million fibers per gram of lung tissue.[110] They found the median lung fiber concentration to be 18 times higher than in a reference group and found fibers in 14 patients with pleural plaques to be 4 times higher than in the same reference group.

Experimental Carcinogenesis

Animal studies using several species and different routes of exposure have produced DMM using chrysotile, crocidolite, anthophyllite and amosite asbestos. Wagner and co-workers reported 11 mesotheliomas occurring after inhalation experiments in rats (four from crocidolite, four from Canadian chrysotile, two from anthophyllite and one from amosite).[111] Roe and associates noted mesotheliomas in mice after injecting them subcutaneously with asbestos fibers.[112] Smith and co-workers induced mesotheliomas in hamsters after intrapleural injection of amosite and chrysotile asbestos.[113] Stanton and colleagues applied amosite, chrysotile and crocidolite asbestos on fibrous glass pledgets to the pleura in rats, obtaining 58 percent to 75 percent incidences of pleural mesothelioma.[114] Wagner inoculated rats intrapleurally with asbestos and other materials producing similar results.[115] Davis studied the histogenesis of mesothelioma resulting from intraperitoneal injection of crocidolite into rats and mice.[116] Many small, pedunculated nodules were noted on visceral surfaces during the early stage. Later, some nodules became large, but most coalesced into a uniform sheet. Berry and Wagner found a larger relative risk in older rats compared with younger rats for DMM when the pleural cavities were injected with crocidolite.[117] Short asbestos fibers have also been found to cause DMM in animal experiments.[118]

Stanton and Wrench have postulated that fine, long, durable fibers correlated best with carcinogenesis using the nonphysiologic technique of pleural implantation.[119] They implanted various fiber sizes and types into the pleural cavity of rats to observe the incidence of DMM. Four types of asbestos, fibrous glass, aluminum oxide, silicon carbide and potassium titanate all produced pleural mesothelioma. He stated that fibers smaller than 0.25 μm in diameter and longer than 8 μm were uncompromised by phagocytic activity, while those considerably shorter or longer were either ingested or sequestered by adherent phagocytes.

Conclusions

DMM appears to be caused by durable fibers with high aspect ratios (length to width). Thin fibers with a diameter less than 1 μm and a length of more than 10 μm appear to be associated with the disease, but many short fibers may induce a tumor as easily as a few long fibers.[118] Amphibole rather than chrysotile fibers are retained in lung tissue, but DMM has the highest relative risk among asbestos insulators in the United States, who are exposed predominantly to chrysotile. Surface properties and fiber (or other substance) interaction may be important. Fiber transport, translocation and retention may be necessary for specific fiber types and sizes to reveal a carcinogenic response. Systemic changes (deranged immune system, affected chromosomes) may identify those at risk or susceptible to the tumor. Treatment has had little success so that understanding the mechanisms of the disease and prevention are likely to be more productive from the public health perspective.

Signs and symptoms of pleural DMM are chest pain, cough and dyspnea, usually with an effusion that can be identified on a chest radiograph. The effusion is an exudate, and cytologic studies are usually nondiagnostic. Open peural biopsy or thoracoscopy are necessary for a diagnosis by histologic techniques. A computerized axial tomographic scan revealing lobulated or encasing tumor and a positive scan using gallium citrate Ga 67 are useful adjunctive tests, especially for determining the extent of tumor involvement. Pleural plaques, per se, do not connote additional risk for DMM beyond the asbestos exposure, although future epidemiologic studies may modify this statement. People with

past asbestos exposure need to be monitored annually for DMM, as well as malignant lesions of other sites, and asbestosis.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Viral/Bacterial Vaccines in the Treatment of Arthritis

QUESTION:

Are there instances in which it is accepted medical practice to administer viral or bacterial vaccines for the treatment of arthritis? If so, please enumerate.

OPINION:

In the opinion of the Advisory Panels of Internal Medicine, Orthopedics and Preventive Medicine and Public Health, there is no new clinical evidence to validate the administration of viral or bacterial vaccines as a treatment for arthritis. The use of such vaccines for this purpose is not acceptable medical practice.

Occupational Epidemiology: Detection of Cancer in the Workplace

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There are fundamental approaches that can be used by health professionals to study the contribution of occupational exposures to cancer occurrence. It would be helpful for clinicians who see patients with cancer to be aware of the methods used to identify those types of cancer that are related to work. Such physicians may be asked by companies or unions to collaborate on the design of epidemiologic studies in work settings or to assist in interpreting results, or they may be consulted by patients from such work environments. Understanding these approaches is essential in order to anticipate, detect and prevent cancer caused by occupational exposures.

That certain types of occupational exposure cause cancer has been known for years. The best known examples involve rare tumors or epidemics so severe that they are easy to recognize; for example, scrotal cancer in chimney sweeps and bladder cancer affecting 60 percent to 70 percent of dye workers. In recent years other unusual tumors have been associated with occupational exposures; for example, mesothelioma in asbestos workers, oat-cell lung cancer in chloromethylmethyl ether workers and angiosarcoma of the liver in vinyl chloride workers. The clustering of these rare tumors did not escape the attention of alert clinicians. These examples represent situations in which the risks are extremely high.

A more difficult problem is to relate occupational exposures to common tumors or to uncommon tumors when the risk is not enormous. These approaches involve quantitative techniques rather than clinical vigilance. For example, showing the relationship between radon daughter exposure in uranium mining and an excess risk of lung cancer required the study of a relatively large population of uranium miners and the use of epidemiologic and biostatistical techniques. This paper will focus on quantitative techniques that can be applied to the study of cancer in the workplace and to observations of associations of tumors with exposures previously thought not to be hazardous. It is written to inform physicians of the uses, applications and limitations of epidemiologic techniques and to demystify some of the epidemiologic jargon.

The debate about how much cancer in humans is caused by occupational exposures usually pits the prototype industrialist, who claims that occupational exposures contribute in a minor way, against the prototype environmentalist, who claims that a large proportion of cancer is caused by environmental or occupational exposure. In our opinion, this debate is fueled largely by ignorance. No one knows. The studies have not been done; the data are not available. Systematic and comprehensive studies, with the involvement of industry, organized labor, government and universities, would begin the work of determining how much cancer is caused by occupational factors. Each discovery of a connection between occupational exposure and tumor production provides basic information that can be applied to reduce the incidence of cancer. This article describes processes and approaches that can be used toward that purpose. The reader who wishes to go beyond the limited scope of this paper is referred to the book *Occupational Epidemiology*.[1]

Conceptual Approach

Epidemiology is a word that many people misunderstand. In this paper, we are simply talking about trying to relate an occupational exposure to a measure of disease, namely cancer incidence or mortality. Does

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chemical X cause tumor Y? To answer that question we need a measure of exposure and we need a measure of cancer incidence or mortality. Optimally we would like information that would allow us to establish a dose-response relationship: How much X causes how much Y?

Exposure or Dose

In most studies of the relationship of a working population to cancer, the exposure or dose side of the dose-response relationship has been neglected or underemphasized. Too little effort has been expended toward categorizing relevant exposure by type, intensity and duration. The exposure that is relevant to cancer is that which occurred years before the onset of the cancer. However, in most work environments few retrospective data on exposure exist. If we walk into a rubber factory, it is difficult to ascertain what the exposure levels have been for the last 20 or 30 years. However, we can estimate the type and intensity of exposures if we know how the industrial processes have changed. Sometimes an epidemiologist can find factories that have not changed or can simulate previous work conditions so that exposure measurements can be made. By characterizing present and future exposures, we can provide valuable information for medical surveillance and prospective studies. Often the best an epidemiologist can do is to determine whether exposure took place—that is, classify workers into exposed and nonexposed groups. The duration of exposure is usually known, so this index of exposure can represent an estimate of lifetime dose.

Tumor Outcome or Response

A simpler part of the equation is counting the cases of cancer. Sources of data on cancer occurrence in populations include local cancer registries, death certificates for a group of workers or death benefit forms in company or union files. While some death certificates are inaccurate and there can be some misclassification of cancer by histologic type, these sources of cancer incidence and cancer mortality information are a solid enough basis to make the associations that are important.

Inherent Difficulties in Population Approach

The importance of assessing exposure has already been stressed, but there are difficulties that must be considered. For example, the *induction period* for tumor development is usually years long. This makes the relevant exposure remote from the incidence or onset of the tumor. Most malignant lesions caused by occupational exposures have induction periods ranging from 12 to 50 years. Because the causative exposure can have occurred during a long period, there may have been many changes in the working environment. In addition, records are often lost, or the worker may have forgotten the materials and processes used in the work. Job mobility also complicates estimation of exposure; that is, the worker may have had several jobs in several locations during the induction period. Frequently, to protect trade secrets, companies are reluctant to release a list of ingredients in materials. In many instances, information on industrial hygiene has not been routinely collected over the last 30 or 40 years, making quantification of exposures difficult. When quantitative data are not available, we often rely on qualitative information; that is, someone was exposed to asbestos at unknown levels for a known period of time.

Other complications in relating exposures to disease result from confounders and competing risks. For example, to ascertain the relationship between an occupational exposure and the incidence of lung cancer, epidemiologists must consider smoking habits. In retrospective studies, detailed information on smoking habits is rarely available although more generalized studies, such as population surveys ascertaining smoking habits by occupation and by socioeconomic status, allow estimation of the effect of smoking. By knowing the smoking patterns of specific occupations and by knowing the relationship between smoking levels and lung cancer incidence, adjustment for smoking factors can be made in any population.

There are several other potential confounders; for example, diet as it relates to the incidence of stomach cancer or other tumors of the alimentary tract. Avocational exposures are frequently important and can confound any apparent result between occupational exposure and tumor incidence. For example, a person who has a hobby of restoring furniture may be exposed to solvents such as benzene that could result in the development of leukemia. Other possible confounders include air pollution, physical activity, stress and drugs.

Another important issue is threshold versus nonthreshold relationships. Policymakers are currently debating about how to deal with carcinogens. If a certain amount of exposure is needed to increase the incidence of cancer, exposure might be permitted at levels below the point at which risk is increased. On the other hand if any exposure increases the risk, no exposure should be allowed. Rarely do data exist that allow scientists to determine whether there is a threshold or nonthreshold situation.

Uses of the Quantitative or Epidemiologic Approach

As noted earlier in this paper, rare tumors occurring at great excess can frequently be detected in clusters; however, common tumors cannot. By following the population in a certain occupational setting, tumor incidence and mortality can be determined. Given the right population and information on exposure, relatively small risks can be detected by the population approach and researchers can ascertain whether occupational exposures are causing common tumors. Although a large population with possible exposure to some substance or substances might have an excess risk, knowledge of specific exposure within the population might allow the identification of a subpopulation with much higher risks. For example, when a large cohort of rubber workers was studied, results showed no striking excess in cancer frequency for any tumor site. However, when the population was broken down by department in

which they worked (where exposure becomes more discrete), excesses of stomach and colon cancer cases were found in those working in the rubber-compounding area, and lung cancer was excessive in workers from the tire-curing area.

Well-done epidemiologic studies frequently provide information on dose-response relationships, such as the studies relating work in uranium mines and with asbestos to increases in lung cancer. Population approaches allow epidemiologists to examine latency or induction periods.

Types of Population Studies

There are three common approaches to studying populations that might be occupationally exposed to elements that possibly increase tumor risk.

1. A population exposed to a specific substance or substances can be followed to determine the number of tumors that develop. Such a *cohort* study allows an epidemiologist to relate all possible health outcomes to a specific exposure or set of exposures.

2. On the other hand, the starting point can be persons with a specific type of tumor. Here the epidemiologist would attempt to determine what exposures have occurred in that group of persons that might explain the cancer. In this instance, the patients with cancer (*cases*) would be compared with similar persons without cancer (*controls*) and past exposures would be ascertained. This approach is called a *case-control* study.

3. In some instances records may exist of the deaths of all workers from a certain company, union or other group. By using the death certificates, cause of death can be compared with the expected *proportions* of mortality based on age, race, sex and time of death. This is called a *proportional mortality* study.

There are advantages and limitations to these three basic approaches that will be discussed in the next section.

Cohort Studies

Most studies of working populations aimed at identifying the relationship between occupational exposure and cancer use the cohort approach. A cohort study has the advantage of providing information on which cancer rates (new cases or deaths) can be computed. By starting with a denominator population with no cancer and following it, a researcher can determine the number of cancer cases that occur and how many deaths result from cancer within that population, thus providing a rate of cancer incidence or mortality. The occurrence of nonmalignant disease can also be examined by this approach. The major disadvantages are that cohort studies can be very time consuming and expensive because many persons must be traced and mortality information collected. Most cohort studies are done by epidemiologists attempting to identify a cohort exposed to some substance of interest 20 or 30 or 40 years earlier, and to follow that cohort forward in time to the present.

In order to do the cohort study a researcher needs a cohort defined in time. For example, all of the shipyard workers employed from 1942 through 1945 might be followed to determine the incidence of mesothelioma that could be related to asbestos exposure in the shipyards during World War II. Once the cohort is identified, the basic procedure is to follow all of those workers to determine their vital status and to collect death certificates or other tumor incidence information for comparison with a reference population. The reference population might be the entire United States, the state in which the cohort lived or, in some instances, the county of work or residence when county data are available for comparison. A cohort study is normally done when there is an exposure of interest and the suspected outcome is a common tumor.

TABLE 1.—*Example of Cohort Study**
Observed and Expected† Deaths Among a Cohort of 13,571 Rubber Workers‡

Cause of death	*ICD No.‡*	*Observed Deaths*	*Expected Deaths*	*SMR§*
ALL CAUSES	...	5,079	6,090.6	83
All cancer	140-205	986	1,064.9	93
Digestive	150-159	368	364.1	101
Stomach	151	98	90.4	108
Large intestine	153	104	103.4	101
Respiratory	160-164	255	293.4	87
Genitourinary	177-181	155	159.6	97
Bladder	181	48	39.5	122
Lymphatic and hematopoietic	200-205	105	94.4	111
Leukemia	204	55	42.7	129
Vascular diseases of central nervous system	330-334	493	524.0	94
Circulatory diseases	400-468	2,448	2,871.8	85
Respiratory diseases	470-527	218	327.0	67
Digestive diseases	530-587	217	279.0	78
Genitourinary diseases	590-637	75	135.8	55
Accidents, poisoning, violence	800-999	279	440.1	63
Residual		363	448.0	81

*The results are presented on a large cohort of rubber workers.[2] While none of the standard mortality ratios (SMR's) for the entire group are very remarkable, further analysis by type of job showed excesses of cancer that could be explained by exposures in those jobs. Note that the starting point is a cohort of 13,571 rubber workers of whom 5,079 died over about 25 years.

†Expected deaths computed on basis of age-time-cause specific mortality rates for US white men.

‡International Classification of Disease, 7th Revision.

§Standardized mortality ratio = 100 × observed number of cases/expected number of cases.

The more precisely exposure can be identified, the better the chance of relating exposure to disease. The example given in the previous section on the "Uses of the Quantitative or Epidemiologic Approach" illustrates this point. Table 1 shows the results of a large cohort study that classified exposure by (1) work in a company and (2) work in specific departments of the company. The mortality (standard mortality ratio) is expressed as a simple ratio of the observed number (×100) of deaths in cohort to the expected number of deaths in white men in the United States.

Case-Control Studies

While cohort studies are based on company (and sometimes union) records, case-control studies are

The Hazard Evaluation System and Information Service: A Physician's Resource in Toxicology and Occupational Medicine

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Hazard evaluation is an emerging science. The Hazard Evaluation System and Information Service (HESIS), part of California's program in preventive occupational health, is a resource for clinicians who wish to stay abreast of the relationship between toxicology and occupational health. For example, advances in assays for cancer or reproductive effects in test animals enable us to identify with greater confidence significant cancer or reproductive hazards among the increasing variety of workplace exposures. Occupational experiences with dibromochloropropane (DBCP), Kepone, bis(chloromethyl) ether, benzidine and vinyl chloride demonstrate the shortcomings of relying on human data. The latency period of cancer, limited sensitivity of epidemiologic studies and severity of effects require us to use animal test data to evaluate the potential cancer and reproductive risks of workplace substances. HESIS gives appropriate weight to experimental data in hazard evaluations of chemicals such as ethylene oxide, ethylene dibromide, polychlorinated biphenyls and the glycol ethers. A similar approach is apparent in the California Department of Health Services' recently released Carcinogen Identification Policy.

In 1977 male workers engaged in formulating commercial batches of several pesticides, including the nematocide dibromochloropropane (DBCP), at a chemical plant in Lathrop, California, realized that for several years none of them had fathered a child. Their fears of apparent infertility were confirmed when, with the cooperation and assistance of their union, the company and health professionals, semen analyses were conducted and the group was found to have an abnormally high prevalence of oligospermia (low sperm count) and azoospermia (absence of sperm).[1] The frequency and severity of these effects correlated well with the duration of the men's exposure to DBCP. Pronounced effects on spermatogenesis occurred at exposure levels as low as 0.4 ppm (eight-hour time-weighted average), doses that produced no other clinical signs of toxicity.[2]

Shortly thereafter, results from the National Cancer Institute Bioassay program were released showing that DBCP caused cancer in test animals at doses very close to those that workers at Lathrop might have received.[3] In addition to being a potent carcinogen, DBCP was also shown to be genotoxic in several short-term tests for mutagenicity using bacteria[4-6] or mammalian cells.[7,8]

The DBCP incident was the first documented example of workplace-induced reproductive failure in men. The rapidly differentiating reproductive tissue in male test animals seems to be particularly sensitive to certain chemicals (see Ethylene Dibromide later in this paper) as is the differentiating fetal tissue in pregnant women (see Glycol Ethers). Public concern was heightened by the discovery that studies were published 18 years earlier showing that DBCP caused testicular

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ABBREVIATIONS USED IN TEXT

DBCP = dibromochloropropane
HESIS = Hazard Evaluation System and Information Service
TIRS = Telephone Inquiry Response System

changes in test animals at dose levels close to those that produced similar adverse spermatogenic effects in the men.[9] Had greater significance been attached to these results in test animals, the reproductive failure in workers at Lathrop might have been avoided.

What can be done to help prevent similar episodes from occurring in the future? Two lessons may be learned. First, the release of information at the right time (for example, animal toxicity data on DBCP to plant officials and workers at Lathrop) could be an effective part of a program of preventative occupational medicine. Second, greater weight may need to be given to results from studies in test animals as predictors of effects in humans.

Shortly after the DBCP episode, the California legislature moved to strengthen the state's academic resources in occupational health and medicine by establishing several Occupational Health Centers on campuses of the University of California. Right-to-know legislation in California was enacted to enable employees and employers to receive information on the hazards of workplace substances and to permit employees (or their physicians) to have access to personal medical records. Finally, the legislature created the Hazard Evaluation System and Information Service (HESIS) within the State's Department of Health Services.*

Hazard Evaluation System and Information Service

HESIS practices preventive occupational medicine by providing information to workers and employers on the health effects of toxic substances used in workplaces and by assisting alert and concerned clinicians in identifying possible occupational determinants of disease. The HESIS scientific staff of occupational health physicians and PhD toxicologists attempts to bridge the gap between the published scientific and medical literature and the workplace community (employers, employees and health professionals) by a systematic review of current issues of 57 journals in toxicology, epidemiology, occupational medicine and related fields. These resources are present in the HESIS library. To provide the most up-to-date information possible on questions of toxicology and occupational health, the HESIS computer provides access to bibliographies of the world's published medical and toxicologic literature, US-sponsored research in progress and numerous medical, toxicologic and occupational health data bases.

HESIS provides information to the occupational health community in several ways. A Telephone Inquiry Response System (TIRS) is available to answer questions from employees, employers or health professionals about clinical symptoms or about toxic substances encountered in California's workplaces. HESIS staff, including scientists, health educators and a librarian, responded to over 1,000 such inquiries in 1981. Such calls may alert the medical community to new health hazards or may trigger follow-up investigations or remedial consultations.

TIRS serves as a listening post for the health problems of California's workplaces. With TIRS and a continual review of the scientific and medical literature and of data from various health registries (such as data on tumors and birth defects), HESIS has begun to create a reasonably comprehensive occupational health surveillance system for California. The cooperation of physicians is needed to improve and extend this system.

From such surveillance, HESIS on occasion conducts an in-depth investigation of a targeted substance, group of substances, health effect or occupation, and releases a written review of the scientific and medical evidence that documents the potential for hazard.[10-22] Following this evaluation, HESIS may inform the workplace community of any new or unappreciated health hazard by issuing a *Hazard Alert*,[23-25] *Information Bulletin*[26] or *Fact Sheet for Physicians*,[27-33] depending upon the apparent severity of the problem. As a consequence of such a hazard evaluation, HESIS may also recommend to Cal-OSHA that the work practices or permissible exposure level (PEL) for a substance be changed (examples are ethylene oxide [EtO],[23] glycol ethers[24] and ethylene dibromide [EDB].[25])

Cancer and Reproductive Hazards in the Industrial Chemical World

Over the past 40 years the production of synthetic organic chemicals has increased enormously (greater than 300-fold),[34] and workers are exposed to a much greater variety of chemicals than ever before. Few of these approximately 50,000 substances have been tested for their ability to cause such severe and life-threatening effects as cancer, mutation, birth defects or sperm damage. For those that have been studied, it has not been clear how animal test data, which provide most of the evidence, should best be used.

The long latency period of some human cancer (as long as 20 to 40 years)[35] raises the possibility that past and present workplace exposures will cause increases in cancer among workers in the future. Although the cancer rate of the general population at present appears to be relatively stable, lung cancer has increased significantly over the last 80 years.[36] The major portion of this increase is attributed to increased cigarette smoking,[37,38] but the contributions of occupational factors are less clear.[37,39] What *is* clear is that significant increases in cancer have occurred in certain workplaces during this same period—such as exposures to bis(chloromethyl) ether, asbestos, 2-naphthylamine and benzidine—without causing visible changes in the cancer incidence in the general population, and that unacceptably high cancer risks were experienced by indi-

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vidual workers from their exposure to carcinogenic agents.

Most of the known human carcinogens to which the public may be exposed have been identified by the high cancer rates observed among workers in specific industries: of the 36 agents for which there is strong or conclusive epidemiologic evidence of carcinogenic effect in humans, 26 were identified by occupational exposures; the remainder are mainly agents used in cancer chemotherapy (see Table 1).[40]

Although less time may be required to see the effects in workers from exposures to mutagenic or reproductive toxins, very little is known about the prevalence of these effects in workplace situations.[41] Effects on spermatogenesis have been studied for occupational exposures to only eight chemicals; clear or suggestive evidence is present for four chemicals other than DBCP[1,42-44] (lead,[45] carbon disulfide,[46,47] carbaryl[48,49] and dinitrotoluene/toluenediamine[50]); and no effects were seen with three others: polybrominated biphenyl (PBB),[51] p-*tertiary* butylbenzoic acid[52] and epichlorohydrin.[42] Adverse reproductive effects in male and female workers have been associated with workplace exposures to several substances.[53] In some cases, spontaneous abortions may arise from damage to sperm cells (see Table 2).

Cancer and reproductive disabilities are serious health hazards. They compel us to regulate workers' exposures to toxic substances and to use animal data where possible to prevent such outcomes from occurring in humans.

TABLE 1.—*Chemicals, Groups of Chemicals and Industrial Processes That Are Carcinogenic or Probably Carcinogenic to Humans*

Carcinogenic

4-Aminobiphenyl
Arsenic and certain arsenic compounds
Asbestos
Manufacture of auramine
Benzene
Benzidine
N,N-bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)*
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
Chromium and certain chromium compounds
Diethylstilbestrol*
Underground haematite mining
Manufacture of isopropyl alcohol by the strong acid process
Melphalan*
Mustard gas
2-Naphthylamine
Nickel refining
Soots, tars and mineral oils
Vinyl chloride

Probably Carcinogenic

Acrylonitrile
Aflatoxin*
Amitrole (aminotriazole)
Auramine
Beryllium and certain beryllium compounds
Cadmium and certain cadmium compounds
Carbon tetrachloride
Chlorambucil*
Cyclophosphamide*
Dimethylcarbamoyl chloride
Dimethylsulphate
Ethylene oxide
Iron dextran*
Nickel and certain nickel compounds
Oxymetholone*
Phenacetin*
Polychlorinated biphenyls
Tris(1-aziridinyl)phosphine sulphide (thiotepa)

*Evidence for effects in humans was obtained from nonoccupational exposures. Adapted from IARC, 1979.[40]

Assessment of Reproductive Hazards: The Value of Animal Data

The DBCP incident raises an important question: How can test results from studies of substances in ex-

TABLE 2.—*Adverse Reproductive Effects Reportedly Associated With Occupational Exposures**

Chemical	*Reported Effects*
To Women	
Laboratory solvents[54-56]	(Chromosome aberrations); (birth defects)
Lead and/or other smelter exposures[57-60]	Spontaneous abortions; reduced birth weights; (congenital abnormalities)
Mercury (metal)[61]	(Abnormal ovarian function)
Anesthetic gases[62-70]	Spontaneous abortions; reduced birth weights; congenital malformations
Phthalate esters[71]	(Anovulation); (increased spontaneous abortions)
Formaldehyde[72]	Menstrual disorders; (increased spontaneous abortions); reduced birth weights
Carbon disulfide[73,74]	Menstrual disorders; increased spontaneous abortions; (reduced fertility)
Organochlorine pesticides[75-77]	(Abnormal ovarian function); (increased toxemia of pregnancy); (impaired lactation)
Benzene, toluene xylene[78]	Prolonged menstrual bleeding
Pesticides (various)[79-83]	Chromosome aberrations
To Men	
Dibromochloropropane (DBCP)[1,2,43,84,85]	Infertility, azoospermia, oligospermia
Lead and/or other smelter exposures[45,57,86-88]	Spontaneous abortions; premature births; [chromosomal abnormalities]; sperm abnormalities
Vinyl chloride[89-95]	[Chromosomal abnormalities]
Anesthetic gases[65,66,68]	Increased spontaneous abortions; congenital abnormalities
Kepone[96]	Loss of libido; reduced sperm counts
Carbon disulfide[47]	Decreased libido; impotence; increased sperm abnormalities
Ethylene dibromide[97]	(Decreased fertility)

Evidence is weaker for reported effects in ( ).
Events reported in nonreproductive tissues in [ ].

*Adapted from Council on Environmental Quality.[53]

TABLE 3.—*Comparison of Reported Teratogenic Effects in Humans and Experimental Animals for Seven Agents**

Agent	*Reported Sites in Humans*	*Reported Sites in Animals*
Anesthetic gases	Hemangiomas, hernias, skin, heart	Skeletal defects only: rat, mouse
Smelter emissions (lead and/or arsenic)	Multiple malformations	Multiple malformations: rat, mouse, hamster (lead and arsenic)
Polychlorinated biphenyls	Skin discoloration; enlarged fontanelles	Skin discoloration and lesions: rhesus monkey; enlarged fontanelles and syndactyly: pig, dog
Alcohol	Facial, central nervous system	Facial, dermal, neural, extremities: rat, mouse
Vinyl chloride	(Neural tube)	Various, including encephalocele: rat
Diphenylhydantoin	Cleft lip, cleft palate, other craniofacial, mental deficiency	Cleft lip, cleft palate, syndactyly, other skeletal defects: mouse; minor kidney anomalies: rhesus monkey
Methylmercury	Central nervous system	Central nervous system, skeletal: rat, mouse, hamster, cat

Evidence is weaker for reported effects in ( ).

*Adapted from Council on Environmental Quality.[53]

TABLE 4.—*Comparison of Lowest Effective Doses of Eight Teratogens in Humans and Animals**

Chemical	*Species*	*Ratio of Animal Dose: Human Dose*
Thalidomide[102,103]	Rabbit	5.0-2.5
Polychlorinated biphenyls[104,105]	Rhesus monkey	1.8
	Dog	14.3
Alcohol[106,107]	Rat	3.8-7.6
Aminopterin[108,109]	Rat	2.0
Methotrexate[110,111]	Rat	4.8
Methylmercury[112-114]	Cat, rat	50.0
Diethylstilbestrol (DES)[115,116]	Rhesus monkey	10.0-2.5
Diphenylhydantoin[117,118]	Mouse	25.0

*Adapted from Council on Environmental Quality.[53]

perimental animals best be evaluated and communicated so as to protect worker health? The interspecies comparisons that can be made between humans and animals for reproductive endpoints (such as spermotoxicity and teratogenicity) are interesting but are based on very limited data. Comparisons that have been made for semen parameters (counts, motility or morphology) between at least two species (including man) show a reasonably similar response for 24 chemicals.[98] Epidemiologic and laboratory studies that assay for semen quality (counts, morphology, or motility) in humans or animals are relatively easy to conduct and quite sensitive. If appropriate human study populations can be identified, a more meaningful comparison between the spermotoxic effects of chemicals in animals and humans may be made in the near future.

Teratogenicity

For teratogenic or embryotoxic endpoints, several thousand substances have been tested in experimental animals, and several hundred have been found to give a positive result.[99] Only a handful have been studied in humans, and fewer of these produce effects.[100] The infrequency of teratogenic events limits the sensitivity of epidemiologic studies, and makes it unlikely that the number of identified human teratogens will increase substantially in the near future.[101] Thus, our knowledge of the predictive value of animal teratogenicity data will likely remain limited. Nevertheless, for the several agents that have been examined, comparisons of their teratogenic *effects* and *potencies* reveals that the human and animal responses are not as dissimilar as might have been expected (see Tables 3 and 4). Thus, for reproductive toxins in general, there may be more of an overlap than we had imagined between agents that affect humans and those that produce effects in test animals.

Cancer Prevention in the Workplace

A first step in limiting cancer risks to individuals and the working population is to reduce the causes of major varieties of cancer—lung, colon-rectal and breast—and control exposures to specific cancer-causing substances. The major *identified* causes of lung cancer include tobacco smoke and asbestos,[38,119] and diet is believed to play an important role in breast and colon-rectal cancer.[120] In theory, cancer may be prevented by modifying the diet, controlling the use of tobacco and reducing exposures to cancer-causing substances such as asbestos. As a practical matter, involuntary environmental or occupational exposures may be easier to control than has been the voluntary use of tobacco or improper diet.

While attention has been focused on assessing the relative proportion of present and future cancer incidences that are caused by *either* "lifestyle" or occupational and environmental factors[37,39] (with varying estimates that need to be resolved by future studies[39]), an uncertainty of perhaps greater public health consequence may be overlooked. The effect of simultaneous exposures of workers to *both* factors, as is likely to occur in the workplace and in everyday life, is more relevant to an appropriate assessment of human risk. In two well-documented human studies of cancer risks from exposures to agents singly or in combination (cigarette smoking and exposures to asbestos or radiation), the cancer risks from the combined exposures are the *product,* not the sum, of the risks from separate exposures. Thus, prolonged cigarette smoking is associated with a tenfold increase in the risk for bronchial carcinoma (lung cancer) while prolonged heavy occupational exposure to asbestos is associated with a fivefold increase in risk. However, combined exposures

(such as cigarette smokers exposed to asbestos) are associated with a 50-fold, and not 15-fold, increase in risk over that experienced by nonsmokers with no asbestos exposure.[119] There are data to suggest that a similar synergism exists between exposures to tobacco smoke and radiation.

Such synergistic interactions may be more common than is currently appreciated, but at present we cannot predict whether the effects of other interactions will be additive, multiplicative or inhibitory. Thus, from a policy as well as a scientific standpoint, the dichotomy between "lifestyle" and environmental and occupational factors may be more artificial than helpful. A simpler view is that cancer has a multiplicity of interacting causes, including "lifestyle" and environmental and occupational exposures, and that these will only infrequently be disentangled.

Oncogenes and Cancer

Oncogenes[149-156] have been isolated from tumors of several human tissues (bladder, breast and lung), the sites of the major types of cancer in humans. When introduced into normal cells, these genes transform the cells into a cancerous state. Genes with similar transforming abilities have been isolated from tumors of these same tissues from test animals. Whereas distinctly different cancer genes exist for bladder, breast and lung, it is significant that the oncogenes from human and test animals are virtually identical for a specific tissue. In addition, some of these genes are virtually identical to the cancer-causing genes of the common tumor viruses that produce cancers in animals.

Even more remarkable is the finding that such genes are present in normal cells where they may participate in the maintenance of daily cellular functions. Damage to these genes (or to other controlling genes) by carcinogens or tumor virus infection may stimulate their activity and lead to cancer.

While much remains to be described of the mechanism of action of cancer genes, the recent discoveries suggest a unifying theory of cancer-causation that is gratifyingly simple. Normal cells contain certain genes necessary for normal cellular function. Modification (mutation, rearrangement and the like) of these genes (or of other genes that normally restrain their activity) by carcinogens or tumor virus infection causes them to function abnormally. This genetic misbehavior converts the cell to cancerous growth.

Methods for Identifying Carcinogens

A carcinogen is generally understood to be a substance or agent that increases the frequency (age-specific incidence) of cancer in humans or in other species.[40,121-129] The identification of chemical substances that pose cancer risks to humans is complex and requires integration of information from several scientific disciplines. Evidence that a substance may be a carcinogen comes from four sources: epidemiologic studies in human populations; bioassays in experimental animals; short-term tests for mutagenicity and cell transformation, and similarities in chemical structure to known carcinogens. Procedures for evaluating data from the first three of these methods are reviewed briefly; it should be noted that they provide evidence of different strengths.

Epidemiologic Studies

Epidemiologic studies offer the overwhelming advantage of providing direct evidence for carcinogenic effects in *humans*. They are well suited to identify major causes of cancer in defined populations (cigarettes, asbestos, initial pregnancy late in life and so forth)[130] but are less suited to determining whether a *specific* chemical poses a cancer risk to humans. Even so, epidemiology has identified several important chemical carcinogens (such as benzene, arsenic) before animal tests were done.[40] At present, the International Agency for Research on Cancer states that there is sufficient evidence for the carcinogenicity in humans of 18 chemicals, groups of chemicals and industrial processes, and there is probable evidence of varying strengths for 18 others[40] (see Table 1).

In addition, negative results from well-conducted epidemiologic studies are useful in placing an upper limit of risk for a chemical exposure. They complement the more uncertain quantitative risk estimates made from data from animal cancer tests.

Epidemiologic methods are extremely useful tools. In general, however, they have low sensitivity. For example, when a cohort study population is relatively small (less than 1,000), the study may fail to identify an agent that increases the risk of a specific type of cancer by a factor of less than five to ten. Even large-scale studies may require an increase of more than 50 percent in cancer incidence before an effect is statistically significant. For this reason, negative results in studies of smaller size seldom provide strong evidence that an agent is not carcinogenic. To detect a carcinogenic effect, it may be necessary to have either a very large study population or a smaller-sized population that is exposed for several years to large doses of a potent carcinogen. In addition, such studies are often difficult to conduct, both because appropriate study groups and reliable information about past exposures are limited and because biases and confounding factors are difficult to eliminate. A recent review[131] reports that epidemiologic data do not exist (and are unlikely to be developed in the future) for the vast majority of industrial chemicals that cause cancer in experimental test animals and to which workers are exposed.

In addition, because of the 20- to 30-year latency period of many types of cancer in humans, epidemiologic studies are not suited to warn and protect people from the cancer risks from exposures to new carcinogens. If an early-stage carcinogen has been identified by an epidemiologic study as a cause of human cancer and the exposures are reduced or eliminated, the cancer risk among those previously exposed may remain appreciable for the ensuing 20 to 30 years. Limiting exposure to late-stage carcinogens or promoters can reduce the cancer risk more rapidly—for example, ces-

sation of cigarette smoking appears to modify the risk for lung cancer within five years.[132,133]

Thus, because of the insensitivity of epidemiologic studies, the long latency period of cancer and the difficulty in obtaining an appropriate study population, we are forced to rely heavily on other means of identifying agents which have the potential to produce cancer in humans.

Assessment of Cancer Hazards: The Value of Animal Data

Fortunately, results from animal cancer bioassays appear to be reasonable qualitative predictors of carcinogenic effects in humans, and the laboratory animal bioassay is widely used to indicate the carcinogenic potential of a chemical. Bioassay methods have been standardized in recent years and, except for minor details, there is now general acceptance of test procedures.[125,134-140] Most substances that are carcinogenic in one species of test animal are carcinogenic in a second when adequately tested;[141-148] most substances that are known to be carcinogenic in humans, for which adequate animal data exist, are carcinogenic to animals.[40,146-148] For several recognized human carcinogens—4-aminobiphenyl, bis(chloromethyl) ether, diethylstilbestrol, melphalan, mustard gas and vinyl chloride—the first evidence of carcinogenicity was found in test animals. Only afterwards were cancer effects looked for, and found, in humans.[148] From a scientific standpoint, it seems reasonable to consider substances for which there is evidence of toxic effects in test animals as likely to produce similar effects in humans. Thus, the International Agency for Research on Cancer concludes, "In the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity (i.e., a causal association) in animals *as if they presented a carcinogenic risk for humans*"[40] [emphasis added].

Indeed, recent discoveries in the molecular biology of cancer would make it surprising if carcinogenesis in rodents is greatly different from that in humans. Cancer-causing genes ("oncogenes") and cell transformation maintenance factors have been isolated from rodent tissues and are virtually identical to those found in the corresponding human tissues.[149-156] These findings indicate that carcinogenesis in humans and test animals may be remarkably similar, and they strongly support the belief that test animals are reasonable and appropriate models for understanding the carcinogenic process in humans.

Sufficient evidence presently exists for the carcinogenicity in animals of about 200 chemicals. The International Agency for Research on Cancer considers there is "sufficient evidence" for carcinogenicity for 142 of the 422 chemicals it has assessed in its review process.[40] The National Cancer Institute has concluded that there is "sufficient evidence" of carcinogenicity for 98 of the 190 chemicals evaluated in its bioassay program,[144] some of which are the same as those reviewed by the International Agency for Research on Cancer. As stated earlier, sufficient evidence exists for 18 chemicals that they are carcinogenic in humans.[40]

For most of the 200-odd animal carcinogens for which there is "sufficient evidence," it is unlikely that we will ever know with certainty whether they cause cancer in humans because of the difficulty in obtaining appropriate populations suitable for epidemiologic studies. Since it is unlikely we will ever confirm or deny the apparent carcinogenic potential of these 200 chemicals, it appears prudent in the interim to control exposures to them as if they had demonstrated effects in humans.

Short-term Tests for Mutagenicity, DNA Damage and Cell Transformation

Short-term tests[157-159] generally evaluate the ability of a substance to produce mutations, chromosomal alterations or DNA damage in a test organism, or to induce transformation of cultured mammalian cells. Systems that are used in short-term tests include microorganisms (such as bacteria, yeast and molds), cultured mammalian cells and whole animals. These tests are comparatively inexpensive ($5,000 to $10,000 per battery of short-term tests versus $500,000 for an animal bioassay) and can be completed in a relatively short time. A number of these tests can be done, therefore, with limited resources. They offer the potential for providing useful information on the two most intransigent problems in carcinogenic risk assessment—species differences between rodents and humans, and estimating risks at very low doses. Some short-term tests can be performed with human cells or tissues; and some effects, such as DNA damage, can be measured at very low doses.

Use of short-term tests to predict carcinogenicity is justified on both theoretical and empirical grounds. Many of these tests detect biological activities (mutagenicity and cell transformation) that are believed to be stages of carcinogenesis. Most known animal and human carcinogens have been shown to be mutagenic when tested in a suitable battery of short-term tests, while most noncarcinogens have not.[160-169] Because of this, a battery of tests can be a useful predictor of carcinogenicity. Such a strong correlation may exist because most of the chemical carcinogens tested thus far act by mechanisms that involve DNA damage, though this has not been rigorously proved. The particular relevance of tests that measure cell transformation is based on the observation that transformed cells, when implanted into a receptive animal host (such as a "nude" mouse) will form malignant tumors.

There is a high probability that a chemical that is *positive* in an appropriate battery of short-term tests will prove to be a carcinogen when adequately tested in animal cancer tests. Short-term tests can be used, therefore, to augment evidence for carcinogenicity from animal cancer bioassays that, for some reason, are not by themselves definitive. Short-term tests can also indicate the *potential* for carcinogenic hazard of chemicals not yet tested in animals. At present, short-term tests are not sufficiently standardized and validated to

provid *definitive* information about carcinogenicity or noncarcinogenicity in the absence of other evidence.

Risk Assessment and Hazard Evaluation

Quantitative estimates of cancer risks in humans based on extrapolation from animal data are difficult to interpret but are routinely made. What information needs to be developed to permit meaningful estimates of cancer risks from exposures to combinations of chemicals such as occurs in occupational settings? What is a reasonable occupational health policy in the interim? Some principles are emerging. Although differences may exist between species in host responsiveness (differences in pharmacokinetics and DNA-repair efficiencies, for instance), the carcinogenic potencies of chemicals in different species of test animals (rats and mice) are generally similar.[170] Moreover, the responsiveness of test animals is reasonably similar to that of humans for those chemicals (21) that have been examined.[170,171] Clearly, the inadequacy of human exposure data limits the accuracy of such comparisons. Such *inter*species differences as exist between rodents and humans must be viewed in relation to the presumed large variation among individuals (such as genetic heterogeneity and host-response differences) in the human population.

Information is needed to improve the accuracy of quantitative estimates of cancer risk from exposures to combinations of agents. In the interim, carcinogenic risks to humans exposed to single or combinations of chemicals must be estimated by extrapolation from available bioassay data using suitable (such as a multistage model) methods, while acknowledging that such methods will *underestimate* the true risks if synergisms occur. Compared with the population of test animals, the population of workers is genetically diverse and is simultaneously exposed to a large number of chemicals. Suitable corrections for these differences also should be made in any appropriate risk calculations.

Summaries of hazard evaluations carried out by HESIS for several substances are given below. The evidence for carcinogenicity or reproductive toxicity of these chemicals is based largely on results from studies in test animals.

Ethylene Oxide

Ethylene oxide[10] is a gas that is familiar to most health professionals as a widely used sterilant for heat-sensitive hospital supplies and equipment.[10] Recent studies have indicated that it is carcinogenic by inhalation in male and female rats (leukemia) at dose levels below the current permissible exposure level (50 ppm).[10,172] It is also mutagenic in 13 test systems,[10] including mammalian somatic cells (micronucleus test)[173] and germ cells (dominant lethal[174,175] and heritable translocation tests).[175] In addition, increased frequencies of sister-chromatid exchanges are found in the chromosomes of workers exposed to ethylene oxide[176] at doses less than one-tenth of the current permissible exposure level.[177] Similar chromosomal effects are produced in test animals (monkeys and rabbits).[178] Adverse reproductive effects (reductions in litter size of exposed female rats at 100 ppm,[179] and sperm count in monkeys at 50 ppm)[10] are evident in test animals at dose levels close to the permissible exposure level.

There is inadequate epidemiologic evidence to assess the carcinogenic or adverse reproductive effects of ethylene oxide in humans.[180-183] However, because of the extensive evidence for genotoxicity in test animals, HESIS issued a Hazard Alert[23] on this chemical and recommended that the permissible exposure level be reduced and that extensive programs in equipment maintenance, environmental monitoring, training and education, and medical surveillance be initiated in hospitals using this substance.

Hospitals are not normally considered to be workplaces where exposures to toxic substances occur. However, the example of ethylene oxide indicates that members of the medical community, like workers in other occupational settings, need to be aware of the potential health hazards of toxic substances present in their work environment.

Formaldehyde

Like ethylene oxide, formaldehyde is a gas for which there is extensive evidence of genotoxicity and carcinogenicity. Formaldehyde is carcinogenic in two strains of rats and in one strain of mice (nasal cavity squamous cell carcinoma)[184,185] (Kern WD, Paukov KL, Donofri DJ, et al: Inhalation carcinogenicity of chronic formaldehyde exposure in rats and mice, unpublished data, 1982) at dose levels (6 to 15 ppm) near the current permissible exposure level (2 ppm). It causes DNA damage, mutation or transformation in four test species (bacteria,[186,187] yeast,[188] *Drosophila melanogaster*[189] and mammalian cells[190]) as well as chromosome aberrations in four species.[191] Epidemiologic evidence available at present has not shown a carcinogenic effect of formaldehyde in humans.[192-194] (Fayerweather WE, Pell S, Bender JR: Case-control study of cancer deaths in Du Pont workers with potential exposure to formaldehyde, unpublished report from E. I. Du Pont de Nemours & Co., May, 1982.) However, many of these studies had limited power to detect a significant increase in cancer incidence, and little or no information on exposure levels of formaldehyde was available.

Because the genetic toxicology of formaldehyde is very similar to that of ethylene oxide, it seems reasonable to adopt similarly safe work practices for formaldehyde and extend the health consciousness of the medical community into other work environments. A significant difference between the two chemicals is that formaldehyde is a potent nasal irritant and, thus, has good warning properties whereas ethylene oxide is a nearly odorless, nonirritating substance and, consequently, has poor warning properties. (In fact, a major health hazard from formaldehyde exposure may be respiratory sensitization.)

Ethylene Dibromide

Ethylene dibromide (EDB)[19,20] has major uses as a lead scavenger in leaded gasoline and as a soil fumigant

in agriculture. With the Med-fly crisis in the summer of 1981, a major increase in use of the chemical was proposed to fumigate citrus fruits, cherries and plums as a means of limiting the spread of Med-fly larvae.

HESIS staff had previously targeted ethylene dibromide as a priority chemical because its genetic toxicology was strikingly similar to that of the closely related brominated compound, DBCP.[19,20] Both chemicals are potent carcinogens, mutagens and spermotoxins with effects occurring in test animals at dose levels close to the permitted exposure levels in workers[20] (see Table 5). They are among the most potent carcinogens of the widely used industrial chemicals that have been tested in animal bioassays[192] (see Table 6). Ethylene dibromide and DBCP are carcinogenic in rats and mice of both sexes, producing the same malignant tumors at the tissue of first contact (oral route: stomach squamous cell carcinomas;[3,196] inhalation: respiratory tract carcinomas[197,198]). For ethylene dibromide, these effects occurred between 1 and 10 mg per kg of body weight per day, uncomfortably close to the dose that workers could receive (7 mg per kg of body weight per day)[192] at the then current permissible exposure level (20 ppm).

As with DBCP, the chemical is also a potent mutagen in several short-term tests for mutagenicity, including the Ames *Salmonella* test,[199] and *Drosophila*.[200] Also, like DBCP, it is a proved animal testicular toxin, causing effects on sperm or male-transmitted reproductive outcomes in three species where it is roughly as potent as DBCP (although in different species and by different routes of exposure, see Table 5).[20] To date, there have been no published reports of infertility or induced semen defects in humans associated with exposure to ethylene dibromide.[207,208]

Because of the extensive evidence that ethylene dibromide is a potent carcinogen and testicular toxin in test animals, HESIS issued a Hazard Alert[25] and recommended that the permissible exposure level be reduced (it is now 130 ppb in California). As was the case with ethylene oxide[23] and with the glycol ethers[24] (see below), the Hazard Alert was distributed to all companies, unions and workers in California who had potential exposures to the chemical. It is to be hoped that the lessons of DBCP have been learned so that human disease from exposure to these chemicals need never be observed.

TABLE 5.—*Effects of Ethylene Dibromide (EDB) and 1,2-Dibromo-3-chlorpropane (DBCP)*

	Route	*Dose*	*Effect*
Potent sperm toxins			
DBCP:			
Rats[9]	Inhalation	1.2	↓Atrophy
Rabbits[201]	Inhalation	0.5	↓Count
EDB:			
Cattle[202-204]	Oral	2	↓All
Rams[205]	Subcutaneous	8-14	↓Morphology
Rats[206]	Injection	10	↓Litter size

Species	*Oral*	*Inhalation*
Tumors produced from oral and inhalation exposures to DBCP and EDB		
Mice ♂,♀	Stomach squamous cell carcinomas	Nasal cavity adenocarcinomas
Rats ♂,♀	Stomach squamous cell carcinomas	Respiratory tract carcinomas

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCB's)[14] have received considerable public notoriety as ubiquitous contaminants of our environment. Because they are complex mixtures that are chemically inert, heat stable and nonflammable, they have a variety of uses as dielectric fluids in transformers, hydraulic lubrication fluids, plasticizers and as components in inks, paints and adhesives.[14] They are carcinogenic in male mice (liver carcinomas)[210] and in two strains of female rats.[209,211] They cause transformation of mammalian cells in culture (DH Norback, PhD, and R Weltman, PhD, University of Wisconsin Medical School, oral communication, 1980). However, polychlorinated biphenyls are only 1/100 as potent carcinogenic agents in test animals as ethylene oxide, formaldehyde, ethylene dibromide and DBCP, and the evidence for their genotoxicity is less extensive (see Table 6).

The highly chlorinated isomers of polychlorinated

TABLE 6.—*Chronic Toxicity of Widely Used Industrial Chemicals*

Chemical	*1981 US Production (in millions of lbs.)*	*Use*	*Carcinogenicity* — *Response* — *Rats*	*Mice*	*Relative Dose to Produce Response**	*Mutagenicity (Number of Different Short-Term Test Systems)*	*Permissible Exposure Level (PEL) (ppb)*
1,2-Dibromo-3-chloropropane (DBCP)	Not produced	Fumigant	4+	4+	1	+(5)	2
Ethylene dibromide (EDB)	250	Gasoline additive; fumigant	4+	4+	1	+(3)	125
Ethylene oxide (EtO)	5,000	Intermediate; sterilant	3+	+	10	+(13)	2,000
Formaldehyde (HCHO)	6,000	Intermediate	2+	+	10	+(7)	2,000
Polychlorinated biphenyls (PCB's)	Not produced	Dielectric		3+	100	Cell transformation (1)	
Trichloroethylene (TCE)	130 (1977)	Solvent	+	4+	1,000	+(4)	25,000
Glycol ethers (GE)	1,225	Solvent			...	−(7)	

*Relative dose (mg/kg/day) required to produce significant tumors (DBCP = 1; approximate values).

biphenyls are not readily metabolized in mammalian species, including humans, and tend to bioaccumulate in adipose tissues.[14] Thus, *although the carcinogenic risk is less well established for these chemicals than for the other chemicals already discussed, it is amplified by the long residence time of these agents in the body*. Because of these factors, HESIS recommended[14] that exposure to polychlorinated biphenyls be kept to a minimum.

Glycol Ethers

Glycol ethers[11] are a group of widely used industrial solvents found in cleaning and thinning agents and in coatings such as epoxies, wood stains, varnishes, paint and ink. They also serve as surfactants in various extraction processes and as fixatives in perfumes, cosmetics and soaps.[11]

Recent studies have shown that the glycol ethers and derivatives produce adverse reproductive effects in laboratory animals,[11] although they are negative in a variety of short-term tests for mutagenicity.[212,213] They induced birth defects in the offspring of exposed females and caused retarded sperm development and testicular growth in exposed males in three species (mice,[214,215] rats[215,216] and rabbits[215,216]). These effects occurred by a variety of dose routes (dermal, ingestion and inhalation) and at dose levels that were only slightly higher than the permissible exposure level for these compounds. The congenital defects observed were severe, including neural tube defects in mice (spina bifida and exencephaly)[214] and cardiac abnormalities in rabbits.[216,217] Rabbits were particularly sensitive to the testicular effects of ethylene glycol monomethyl ether, and degenerative changes in the testicular germinal epithelium were evident in one study from exposure to 30 ppm for 90 days (permissible exposure level: 25 ppm)[218] (Miller RR, Calhoun LL, Yano BL: Ethylene glycol monomethyl ether: 13-week vapor inhalation study with male rabbits, unpublished report from Dow Chemical, USA, submitted by the Chemical Manufacturers Association, 1982). Moreover, cardiovascular defects were observed in the offspring of rabbits that received ethylene glycol monoethyl ether.

There is inadequate evidence to assess the reproductive effects of glycol ethers in humans. Women exposed to a variety of solvents, including a glycol ether, reported a variety of gynecological disorders, and their newborn children had a higher incidence of birth defects (including congenital heart defects) than did newborns from a control group.[219] The significance of the birth abnormalities is tempered by the workers' exposures to other solvents.

Because of the severity of the reproductive effects in test animals, HESIS issued a Hazard Alert[24] and recommended that the permissible exposure level for the glycol ethers be lowered and that work practices be changed (use of impermeable gloves, protective clothing and good ventilation) to reduce skin and inhalation exposures. It is noteworthy that male and female reproductive tissues are affected by such nonreactive, nongenotoxic substances as the glycol ethers. Other solvents that share the special hydrophilic and lipophilic solvating ability of these substances could produce similar effects and should be tested.

Conclusions

Research on cancer and reproductive effects is continuing, and as our understanding increases, programs for prevention and control of these diseases will likely change. Prevention, however, can proceed without precise answers, and we must make occupational health decisions based upon the best available evidence. Cancer risks to the working population and to the individual person can be reduced by a comprehensive program to modify the major identified determinants of cancer and to control exposures to specific carcinogenic substances.[220] Similar programs should be possible with reproductive agents. Modification of work practices cannot be constrained to require absolute certainty when the consequences of inaction could result in serious effects on the health and welfare of the working population.

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Industrial Hygiene Data: Compliance, Dosage and Clinical Relevance

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Much of the data collected by industrial hygienists on levels of airborne contaminants in the workplace is of marginal relevance to the needs and interests of physicians practicing occupational medicine. Several factors influence data collection. Regulatory agencies require rigid interpretation of exposure levels, yet concentrations of contaminants in the air environment vary considerably. This discrepancy suggests a different approach to dealing with the regulatory problem, one which recognizes its inherent statistical nature. Increased attention also should be devoted to basing sampling intervals more directly on toxicological measurements. These changes would result in the collection of environmental data of greater relevance to physicians, toxicologists and epidemiologists because such information would allow more realistic estimates of the hazard of a cumulative exposure for a given work population.

The field of occupational health includes physicians, nurses, industrial hygienists and toxicologists who all share the goal of preserving the health of working people. Each of these practitioners uses skills acquired from both formal training and professional experience. For instance, while the physician investigates clinical evidence of damage and disease, the industrial hygienist investigates conditions in the workplace that allow damage and disease to occur. In the following discussion we will analyze how the data gathered from the work environment by hygienists relate to the observations of clinicians. Although the discussion is restricted to chronic exposures to airborne chemicals the conclusions often apply to physical agents as well.

Although industrial hygienists and physicians share an interest in the relationship between exposure and disease, much of the monitoring data that have been painstakingly gathered and catalogued by hygienists are of little utility to physicians. Many industrial hygienists design surveys to comply with regulatory standards rather than to estimate the cumulative doses of chemicals received by workers. By cumulative dose we mean some integrated measure of the total amount of a toxic agent that reaches a receptor site over time. We assume that this amount increases with increasing exposure. From an environmental perspective, the quantity of a substance that is clinically relevant is not the concentration of toxicant in the air at one time, but the concentration summed over a time interval determined by the toxicology of the chemical in question.

Because existing regulatory standards tend to be narrowly focused and rigidly interpreted,[1] monitoring practices today typically yield only a few point estimates of exposure and tend to neglect both the variability of exposures and the kinetics of uptake and metabolism of the chemical in the body. We will illustrate in the following discussion how this trend makes the assessment of cumulative dose extremely difficult.

Regulatory Arena

The regulatory context for evaluating occupational exposures in the United States was defined by the Occupational Safety and Health Act of 1970. This legislation established the Occupational Safety and Health Administration (OSHA), an agency given the authority to set legal limits for chemical concentrations in the air considered safe for workers, and to require monitoring to ensure compliance with these limits.

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ABBREVIATIONS USED IN TEXT

OSHA = Occupational Safety and Health Agency
TWA = time-weighted average

Although there had been guidelines of acceptable exposure levels before the establishment of OSHA, notably the Threshold Limit Values of the American Conference of Governmental Industrial Hygienists, the air concentrations specified had not been legal limits. These earlier guidelines attempted to define levels that should be safe for most workers over a working lifetime and were not interpreted as a fine line separating acceptable and unacceptable conditions. Whether or not the air concentrations of toxic substances specified by the Threshold Limit Values actually provided sufficient protection or whether hygienists applied them appropriately is not clear, yet under the system that prevailed prior to OSHA, the interpretation of air measurements was fairly flexible.

With the entry of OSHA into the picture, standards of exposure to airborne chemicals did define the line between acceptable and unacceptable conditions. This rigidity produced two important effects on the determination of cumulative dose. First, because the limits were interpreted as absolute limits, any measured exposure that was found to exceed the standard was prima facie proof of noncompliance and carried with it both explicit and implicit penalties to the employer.[1] Some penalties, such as the requirement to institute engineering controls, carry great economic implications. Furthermore, because absolute limits cannot be achieved in a theoretical sense,[2] virtually any workplace can be declared out of compliance if the hygienist is able and willing to collect enough air samples. (The probability of declaring noncompliance with an absolute limit is equal to $[1-(1-u)^n]$ where u is the probability that any single exposure would be out of compliance and n is the number of measurements. Note that $[1-(1-u)^n] = 1$ as $n \rightarrow \infty$.) Absolute limits can exist in practice, however, if the number of measurements is reduced to the point where none exceeds the limit (for example, compliance is guaranteed if no measurements are made). Thus, an air sampling scheme can "succeed," in the sense that it declares some but not all workplaces out of compliance, only by fixing or otherwise limiting the number of measurements. This is in fact what OSHA compliance officers and many employer-based hygienists do.

The second problem with OSHA standards is the uniformity of the averaging time used for monitoring. All OSHA standards for chronic or delayed toxicity are based upon an eight-hour time-weighted average (TWA) exposure. This practice ignores the kinetics of uptake of various contaminants in the body which, as shown by Roach,[3,4] varies from seconds to years and is a critical determinant of cumulative dose. We will illustrate later how this rigidity in the selection of averaging time can obscure the determination of hazard.

Exposure Variability and the Estimation of Cumulative Dose

Chemicals are generated and dispersed into the air of a workroom by a variety of means depending on both the nature of the process and the environmental conditions that prevail at the time. The air environment can be viewed as a dynamic system in which concentrations of a contaminant in the air ebb and flow over time according to the combined effects of both random and systematic processes. Thus, a worker's exposure to an airborne contaminant fluctuates throughout the work day as he moves about the work area performing the job.[2]

Industrial hygienists generally characterize airborne exposures by collecting representative air samples in the workroom to determine the levels of contaminants encountered. Historically, most air samples were gathered at fixed locations, and estimates of exposure were based upon the proximity of the worker to the site measured. However, because air concentrations inhaled by the worker often correlated poorly with concentrations at fixed locations where air was sampled, this practice was abandoned in favor of a personal sampling technique employing portable equipment worn by the worker. The change to the personal sampling technique allowed hygienists to control for spatial variability of contaminant levels in the workroom but still did not control for fluctuations in exposure over time.

It is this uncontrolled temporal variability that leads to uncertainty in the estimation of cumulative dose. For instance, if eight-hour TWA exposures are measured for a certain worker over 100 days, the range would probably cover between one and two orders of magnitude. (It is often assumed that workers' exposures are approximately lognormally distributed. If one worker's eight-hour TWA values measured over 100 days were derived from a lognormal distribution with a geometric standard deviation of 2.5—which is typical of what is often encountered—the highest measured TWA value would be approximately 70 times the smallest measured value.) Whenever estimates of daily exposure are based upon only a few measurements (fulfilling the minimum requirement of regulatory agencies), the temporal variable is ignored and little insight is gained concerning the cumulative distribution of exposures. Thus, one deficiency of the industrial hygiene data base is that it often contains only exposure estimates at a few discrete times. There is no clear indication of how these data might be integrated over time in a way that will allow physicians to gain a picture of the effect of cumulative exposure.

The Relationship Between Exposure and Clinical Response

In order to formulate a data collection scheme that would allow a physician, a toxicologist or an epidemiologist to make reasonable inferences regarding the nature and magnitude of the dose received by a worker or group of workers over time, the functional relationships between duration as well as concentration of exposure must be quantified. Figure 1 shows these

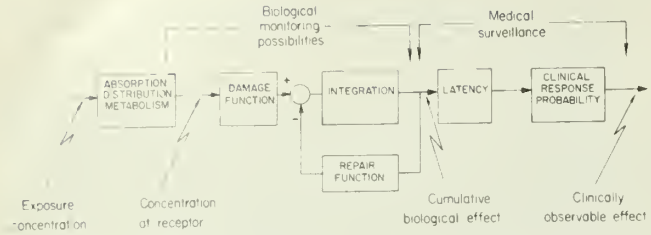

Figure 1.—Functional relationships between chronic exposure to an airborne chemical and biological response in the exposed population.

relationships schematically. The first box contains the toxicologic version of the pharmacodynamics of the process, including the kinetics of absorption, distribution, metabolism and excretion of the toxic agent. The output of this box is assumed to be the concentration of the agent or its metabolite that interacts at the receptor site to produce "damage," the particular functional relationship being contained in the second box. It is assumed that the output of the box labeled "damage function" is proportional to the rate at which damage is being produced. Similarly, repair processes are operating at a rate which, when subtracted from the damage rate, gives the net rate at which damage or repair is occurring at any particular instant. Integrating this net rate over time gives the cumulative effect of the toxin on the biological system. The box labeled "latency" indicates that for many toxins the expression of the accumulated effect is often delayed in time. The final box represents the relationship between this accumulated effect and the probability that it will be manifested as a clinically detectable response.

It is evident from Figure 1 that for air monitoring data to be a useful indicator of clinical response, the averaging time of measurements must be correlated with the kinetics outlined in the first box. The implication of basing all measurements upon eight-hour exposures, as is currently done, becomes clear. If the kinetics associated with uptake and elimination are quite rapid, being completed in a few minutes, damage would more likely result from brief periods of high exposure, when the concentration at the receptor site is great, than from more-or-less constant but low level exposures even though such an exposure would give the same TWA value after eight hours. In this case, information about transient, high levels of toxicants would be needed to arrive at a satisfactory correlation of exposure with clinical response. If, on the other hand, uptake and elimination of a substance would take months, then damage would accrue very slowly and information about a transient exposure would not be useful. Indeed, because of the inherent noise, such data could obscure the estimation of long-term dosage.

Figure 1 demonstrates that a small number of air samples taken over a period of weeks, months or years is unlikely to adequately define input to the complex toxicologic processes which can themselves extend over years. The question remains—what kind of systematic sampling can adequately define the cumulative hazard to a worker? This problem, one of the central issues of occupational epidemiology, is the key to classifying the worker cohort into exposure categories. In pursuing this goal, suppose that the duration of measured exposures is chosen to reflect the kinetics of absorption and elimination of a contaminant—for example, brief measurements for a rapidly absorbed chemical. Suppose further that a sufficient number of air samples are taken so that the statistical distribution of sample values can be estimated. Under the assumption that the environment is unchanging in terms of its statistical description, the distribution of these values allows one to make some reasonable predictions about worker exposures over longer periods. It is possible to estimate the mean and variance of the cumulative dose for an individual given the total number of days worked and an estimate of that individual's mean respiratory minute volume. With these estimates it is possible, for example, to classify workers into different exposure groups with some statistical justification. Knowing this, the industrial hygienist could conduct an air sampling program, with due regard for randomness and independence, that would allow appropriate estimation of the distribution function of relevant exposures. Such an air sampling program would fulfill the usual industrial hygiene needs while providing data of greater medical relevance.

An Example of This Approach

A study of exposure to ethylene oxide that was conducted by one of us illustrates a desirable approach to obtaining data useful in the development of a cohesive scheme for environmental monitoring.[5] We wanted to characterize workplace exposure to ethylene oxide and to measure a particular biological effect—sister chromatid exchange rate in the chromosomes of the peripheral lymphocytes of those exposed to the chemical—in order to investigate the exposure-effect relation over a defined time of exposure.

A sister chromatid exchange is the visual manifestation of a four-stranded exchange in the DNA. In this instance, sister chromatid exchanges were observed in chromosomes of lymphocytes obtained from peripheral blood. Determining increases in the average number of sister chromatid exchanges per cell is an extremely sensitive method for measuring chromosomal effects of mutagenic/carcinogenic agents and has been used extensively in in vitro screening assays for these compounds; it has correlated well with other short-term tests for DNA damage.[6,7] The exact mechanism of formation of sister chromatid exchanges is currently unknown, as is the clinical significance of increased sister chromatid exchange rates in humans.

Our study was conducted in hospitals that use ethylene oxide as a sterilant for supplies in a setting apparently free of significant exposure to other chemicals. Ethylene oxide is absorbed into the body quite rapidly, with a biological half-life of about ten minutes. Because the exposures to this chemical in the hospitals were infrequent, of short duration, but high concentration (occurring when sterilizers were opened), a portable single-beam infrared spectrophotometer was placed in the area where ethylene oxide was used to measure

and record these short-term exposures of operators as they performed their work. A previous check had determined that there were no extraneous exposures to ethylene oxide caused by such factors as leaking gaskets on sterilizer doors.

In order to express an estimated dose of ethylene oxide received by a worker during a brief exposure, it can be assumed that, because of the solubility characteristics of the chemical, alveolar uptake and absorption of ethylene oxide approaches 100 percent. The expression for estimated mean dose per task $\bar{D}$ (in mg) is then

$$\bar{D} = \bar{V}_m \bar{c} \bar{T}$$

where $\bar{V}_m$ is the mean respiratory minute volume (estimated to be about .021 cubic meter per minute for humans performing light work), $\bar{c}$ is the mean measured concentration of ethylene oxide (mg per cubic meter) and T is the elapsed time (minutes) during task performance. The mean cumulative dose (D_w) received by a worker, again assuming 100 percent absorption of ethylene oxide (in mg) would then be

$$D_w = \sum_{i=1}^{k} \bar{D}_i n_i$$

where n is the number of times each task is performed and k is the number of different tasks.

Table 1 lists the values for a mean cumulative dose accumulated over six months for workers tested in this study and gives the mean levels of sister chromatid exchanges per cell observed for each worker. Analysis of the data given in Table 1 indicated that workers with relatively high cumulative doses (mean cumulative dose of more than 100 mg) had significantly higher levels of mean sister chromatid exchanges per cell ($P<.005$) than those with relatively low cumulative dose (mean cumulative dose of less than 100 mg). More extensive analysis with a control group that was matched with the experimental group for smoking and age confirmed that a detectable shift in cumulative frequency distributions of sister chromatid exchange levels was correlated with mean cumulative dose.[5]

The foregoing example illustrates the general points made earlier in the discussion. First, if the investigation had been performed solely to comply with current OSHA criteria, it is unlikely that sufficient information would have been available to estimate the cumulative doses received by the workers. The existing OSHA standard for ethylene oxide is 50 parts per million as an eight-hour TWA.[9] Using the current OSHA scheme recommended for evaluating exposures[1] the hygienist would have selected one or more of the workers, measured their eight-hour TWA exposures to ethylene oxide for a day or two, and finding them to be less than 1 part per million would have concluded that they were "in compliance," and left it at that. The same conclusion would probably have been reached even if the lower level of 1 part per million (also as an eight-hour TWA), recommended by the American Conference on Governmental Industrial Hygienists[10] had been used. Additional monitoring would not have been required unless the process was changed in the future.

TABLE 1.—*Mean Cumulative Dose Estimates and Mean Sister Chromatid Exchange Rates for Workers Exposed to Ethylene Oxide During a Six-Month Period*

Working Group	*Individual D_w* (mg)*	*Group D_w (mg)*	*S.D.*	*Individual Mean SCE† per cell*	*Group Mean SCE per cell*	*S.D.*
Relatively	0	13	18	7.50	7.76	1.05
Low	0			8.16		
Exposure	0			9.62		
to Ethylene	10			7.24		
Oxide	12			7.76		
	12			6.60		
	12			8.54		
	12			8.28		
	58			6.16		
Relatively	173	501	245	9.64	10.69	1.92
High	384			8.00		
Exposure	461			12.98		
to Ethylene	744			11.16		
Oxide	744			11.66		

*D_w = mean cumulative dose
†SCE = sister chromatid exchange rate

To reiterate, then, the combination of (1) an inappropriate averaging time of eight hours, which obscures the importance of transient high exposures, and (2) the inadequacy of a sampling scheme that is predicated on an absolute limit reduces the possibility of obtaining information of clinical use concerning exposure to ethylene oxide, assuming that the sister chromatid exchange is a response that serves as an index of clinical interest.

Conclusion

Current standards for monitoring toxic substances in the workplace are focused primarily on legal criteria that are incompatible with the collection of clinically useful data. These criteria have two significant shortcomings. First, compliance is defined in terms of absolute air concentrations. As such, the standards present a disincentive for monitoring. For this reason, data establishing cumulative exposure or dosage in the face of great environmental variability are not generally collected. Second, averaging times for monitoring airborne chemicals that produce chronic effects are universally based upon eight-hour TWA values. This practice ignores the importance of the kinetics associated with uptake and effect which can, as illustrated, lead to incorrect assessments of hazard.

The solution to the problem appears to be the adoption of regulatory standards that are more flexible. The notion of compliance monitoring can actually have many advantages. The current situation is undesirable primarily insofar as it discourages the gathering of information related to distributions of exposures. If compliance were defined in terms of the fraction of exposures that *could* exceed a given air concentration, the incentives would be changed to actually encourage the gathering of useful information. This type of standard has been used for

some time in dealing with community air pollution and there seems to be no reason why it could not also be applied to occupational exposures.

Concerning the selection of averaging times, it seems clear that consideration must be given to the rate of uptake of the chemical in the body. Roach[4] has suggested in this context that the optimal averaging time would be three times the biological half-life within the body, because at this duration the normalized temporal variability of the body burden equals that of the exposure regime. Given recent advances in sampling and analytical methods, it should be possible at present or in the near future to accurately measure worker exposures for either very short or very long periods. Thus, it should not be particularly difficult from a technologic perspective for the hygienist to select averaging times that comply with this criterion in the future.

Evaluation of environmental levels of toxic agents in the workplace can be of enormous assistance to clinicians both in diagnosis and prevention of occupational disease, if the data are collected with this use in mind. It may be that it is time for hygienists, physicians and toxicologists to get back together to develop environmental monitoring strategies that are effective, flexible and directed at worker protection in a comprehensive rather than in a narrowly legal framework.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Intermittent Positive Pressure Breathing

QUESTION:

Is intermittent positive pressure breathing, with or without nebulized saline, an accepted preoperative medical procedure for the prevention of pulmonary complications in patients (1) with and (2) without known pulmonary disease?

OPINION:

It is the opinion of the Advisory Panels on Allergy, Anesthesiology, Chest Diseases and Internal Medicine that intermittent positive pressure breathing (IPPB) is not an accepted *preoperative* medical procedure for patients without pulmonary disease except to train patients for possible postoperative use of needed adjuvants against pulmonary complications. For selected patients with pulmonary disease or neuromuscular impairment who need bronchodilators and who cannot take a deep breath or mobilize secretions effectively, IPPB would be an accepted procedure together with other preparations for bronchial toilette.

The Evolution of Occupational Health and the Role of Government

RICHARD WADE, PhD, MPH, *San Francisco*

Concern for the protection of workers' health is not new to medicine. Physicians in the 1400's raised awareness among colleagues as to the need to prevent the diseases of employment in mines. Society has responded to increasing levels of evidence as to the relationships between disease and certain worksites by making employers accountable for the individual and social costs incurred by poor workplace hygiene. This has occurred by the development of workers' compensation and occupational health and safety regulatory programs. The impact of these efforts has been to significantly reduce occupational disease and safety problems in industry. Increasing resources have also been given to the training of physicians in occupational medicine and research into links between occupations and disease. Increasing pressure to reduce public spending and to deregulate are challenging government's ability to continue research, training, technical information distribution, consultation and regulatory cleanup efforts to improve work conditions and thus reduce the incidence of occupational safety and health problems.

Society through its government institutions has a long history of interest in protecting workers. Decisions as to the appropriate role of government in an age of reductions in government intervention are now critical in determining future trends in occupational health. Paracelsus, a Swiss-born nomadic physician (1453-1541), published some of the earliest works on the relationship between respiratory disease and the mining and smelting industries. These monographs led to increased attention to "hygiene" in the mines. Approximately 100 years later the recognized father of occupational medicine, Bernardino Ramazzini (1633-1714) devoted his medical practice to the study of occupational diseases and the advocation of improving the well-being of the working class.

> Medicine, like jurisprudence, should make a contribution to the well being of workers and see to it that, so far as possible, they should exercise their callings without harm. So I for my part have done what I could and have not thought it unbecoming to make my way into the lowliest workshops and study the mysteries of the mechanic arts.[1]

Through the early 19th and 20th centuries, Western European countries made discoveries as to the relationship between occupations and disease. In 1775 Percival Pott showed the relationship between scrotal carcinoma and chimney sweeping. In the United States as early as 1867 Massachusetts began to employ factory inspectors to protect employees from dangerous machinery.[2]

Workmen's compensation programs were developed by states in the early part of this century in response to increasing frequency of industrial accidents and diseases, as the United States was fully in the throes of the Industrial Revolution.[3]

In 1911 the state of Wisconsin made the employer legally responsible for the provision of a safe and healthful work environment.

Between 1911 and the late 1960's, the precedent was being set nationwide as to employer responsibilities to provide safe and healthful work environments for their employees. State and federal agencies adopted varying degrees of enforcement, education and consultative services. During this time, considerable research was done on the acute hazards of various chemicals, especially metals and fibrous materials. During this time, asbestos was established as a respiratory carcinogen and

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persons exposed to such materials during World War II started having clinical symptoms of asbestosis, mesothelioma and carcinoma of the lung.

Professional societies such as the National Safety Council, professional engineering societies, industrial hygiene associations, trade associations and the federal government developed national consensus minimum standards. These consensus standards were used by insurance companies to evaluate work practices of their policyholders, by industry for self-evaluation and by federal, state and local government agencies to evaluate industries on a voluntary basis.

During the late 1950's and 1960's organized labor continued to bring pressure for improved health and safety legislation.[4]

In 1970 President Richard Nixon signed the Occupational Safety and Health Act which established a nationwide enforcement-oriented health and safety program. This legislation called for the development of increasingly stringent standards to be met by all employers. It called for vigorous enforcement of these standards by both state and federal employees.[5]

Scope of the Problem

In 1970 an estimated 25 million workers in the United States were injured on the job or had an occupation-related disease develop. The actual recorded numbers are lower: 14,000 killed and 2,200,000 temporarily or permanently disabled.[6]

Using California data as another indication of the problem's scope, in 1979 for every 100 workers in the state, 10.7 had an occupation-related injury or disease. Thus, 881,000 Californians, or about 10 percent of the daily workforce, are adversely affected by work environment. Based on workers' compensation reports, trauma and occupational injuries represent most of these cases and only 3 percent of all these cases were occupational disease related. Most occupational disease cases showing up in these data constitute dermatitis and acute systemic poisoning cases. Few cases of chronic disease ever appear in these data due to the difficulties of showing cause-and-effect relationships for materials that have long-term latency periods—for example, benzene, asbestos or other mutagens or carcinogens.[7] Even so, these few reported cases cost California employers a loss of 6.2 million work days per year with 74.7 lost work days for every 100 full-time employees per year.

Thus, even with these underrepresentative data, the large scope of the problem can be seen. Efforts to reduce worker exposure to safe levels of potentially hazardous chemicals and physical agents can be seen as a laudable social goal.

Who Is Responsible?

Under federal law, it is the legal responsibility of the employer to provide for a safe and healthy work environment. Social institutions such as the government are merely designed to provide the initiative to ensure that this goal is achieved.

The federal Occupational Safety and Health Act of 1970 was premised on the need for minimum standards and national consistency as to standards and enforcement. Before 1970 each state ran some type of program, with many states having no government programs at all.

The responsibility for occupational safety and health programs in the Western United States is divided between state and federally run programs. The US Department of Labor—through the Occupational Safety and Health Administration (OSHA)—runs the occupational safety and health programs in the following Western states: Montana, Idaho and Colorado. (Nationally, a total of 23 states plus Puerto Rico have state-approved plans.) In the remainder of the states, the occupational safety and health programs are run by the states. In each of these states the state program must prove to OSHA that it is at least as effective as the federally run program and has laws and regulations at least as stringent as the federal program. Once a state has shown its effectiveness, it can apply for 50 percent of its operating budget to come from federal sources. The state program is then evaluated annually to ensure continued compliance with these criteria. Most state-run programs rely almost exclusively on the adoption of federal standards and enforce these standards as part of their state-administered regulations. Most state programs are relatively small and staff are limited to field enforcement plus administrative personnel. The program in each of these states is designed to conform to state-administrative procedures.

Until 1970, there were few national standards and great inconsistency among states. The national act changed all that, setting forth a mandate for tough national regulations and rigorous enforcement without preempting the authority of states to establish higher standards.

Changes in Technology

Standards were developed that forced state of the art changes in engineering design, and monitoring instrumentation to evaluate industrial hazards. For example, air quality 15 years ago was measured by loss of visibility caused by airborne-suspended particulate materials. Now air quality is evaluated by sophisticated sampling devices that measure qualitatively and quantitatively the levels of respirable-sized particles entering a workman's lungs over an eight-hour work shift. Acceptable levels of pollutants have gone from thousands of micrograms of materials per cubic centimeter of air to hundreds of micrograms per cubic meter per day.

Standards have been set which call for engineering controls to be developed (so-called technology forcing). An example of this is development of increasingly lower permissible exposure levels (PEL's) for solvents used in degreasing operations. Early work practices had employees heating solvents such as trichloroethylene and carbon tetrachloride in buckets and working for hours breathing high concentrations of fumes from these acutely toxic and suspected carcinogenic materials. Reducing permissible exposure levels forced manufacturers to develop semiclosed systems that provide mechanical

ventilation and reduced wetted surface areas, thus reducing the employee exposure.

The ultimate goal in any successful occupational health/industrial hygiene program is to reduce employee exposure. Three major options are available to achieve this end: (1) engineer out the problem; (2) provide personal protective equipment so as to provide a barrier between the material and the worker; (3) administrative controls whereby the time of exposure is limited, thus reducing dosage.

OSHA (as well as some state regulatory agencies) places emphasis on engineering out a problem. Occupational noise, a well-recognized cause of significant premature hearing loss, is a classic example of the many problems faced when deciding on engineering controls versus personal protective equipment.

Noise engineering controls consist of either reducing mechanical friction through design changes or by providing noise barriers (enclosures). Where these engineering controls are not feasible, personal protective equipment such as ear plugs and ear muffs are used. These devices, although effective at reducing certain kinds of noises, are often awkward and inconvenient to wear. Thus, it is all too easy to fail to use personal protective equipment resulting in serious and, in the case of noise, irreversible hearing impairment. In some situations, neither engineering controls nor personal protective equipment are adequate to protect all workers. Thus, controlled access to areas of potential exposure, limiting the time one works in a given level of contamination and exclusion of those at greatest risk can all result in reducing effective delivered dosage.

Cal/OSHA

In many ways California's experience with occupational health and safety regulation may be of interest nationally and provide general insights into the role of government in occupational health. Because of the state's large area and population, Cal/OSHA (the state regulatory agency in charge of enforcing occupational health and safety regulations in California) could never expect to have enough staff to inspect the approximately 500,000 places of employment in the state. Cal/OSHA sets the standards in terms of safe and healthful work practices and it is the responsibility of each employer to ensure compliance. Employees, likewise, have the responsibility for compliance with safe work practices set forth by an employer.

Standards Development

The development of standards by Cal/OSHA has two objectives: (1) to set a minimum standard at which an employer must protect employees and (2) to provide an incentive to compliance with that standard. In all cases where Cal/OSHA develops an occupational health or safety standard, two primary issues must be addressed: (1) what constitutes a safe level of exposure and (2) what level of protection is feasible (what can realistically be achieved given existing technology).

Although enforcement provides an incentive and, therefore, is necessary, it is not sufficient to provide adequate work conditions. Most employers in California do comply with developed health and safety standards. Some go far beyond Cal/OSHA standards in government to ensure even greater margins of safety for their employees.

Occupational health is more than regulation. In addition to enforcement in a comprehensive occupational health program, there is a need for employer education, technical consultation with employers, employee education and professional education, and training and improved access to technical occupational health information. With these concerns in mind, Cal/OSHA initiated a system of program development addressing all of these concerns.

Research

California actively participates in occupational health research through a research and standards development unit. This unit is charged with doing the necessary background work to justify the development of a safe permissible exposure level and to substantiate what level of control is technologically feasible. Standards for asbestos, ethylene dibromide and trichloroethylene exposure have been developed, among others. At present, background materials are being prepared for standard promulgation on formaldehyde, ethylene oxide and glycol ethers, as well as for justifying reduction of the permissible exposure levels for more than 40 other existing standards.

Professional Training

A second emphasis is on expanding education and training options for occupational health professionals. The state's Department of Industrial Relations was instrumental in passing a state legislative bill (AB 3414) which called for the development of two Occupational Health Centers. Between the two centers—one in Southern California (University of California campuses at Irvine and Los Angeles) and one in Northern California (San Francisco and Berkeley campuses)—33 faculty members including toxicologists, physicians, occupational health nurses, educators and biostatisticians have been hired. The centers have been the focus of increased occupational health continuing education as well as clinical, basic and applied research. Both centers are now opening outpatient clinics serving the industrial community. The centers are charged with professional education of nurses, toxicologists, occupational medicine physicians and occupational health educators, as well. Faculty from the centers have also served as a technical expert resource for both the private and public sectors.

Employee/Employer Information on Chemical Hazards

In addition to professional education and training, there is also need for the provision of information to employers and employees alike as to the hazards of a particular chemical and how that chemical can be handled safely. In 1977 recognition of sterility in workers employed in the manufacturing of DBCP (dibromochloropropane) showed the need to make health effects

information available to employers and employees. In the DBCP case, there had been information in the scientific literature in 1962 on testicular atrophy and sterility in animals exposed to relatively small doses of this chemical. Employees, however, continued to be exposed to DBCP until they recognized none of them were able to have children. They filed a Cal/OSHA complaint and the subsequent investigation uncovered the scientific information/worker awareness gap. In order to help fill this gap, the Department of Industrial Relations developed a program called the Hazard Evaluation System and Information Service (HESIS), designed to systematically search the scientific literature and to make information available to all interested parties. In addition to responding to inquiries, this unit also periodically sends out hazard alerts to the employer and employee community.

Emergency Toxic Chemical Information

Increasingly, the public sector is being asked to respond to chemical emergencies such as explosions or spills involving toxic chemicals. To this end, information must be made available to the responding parties (fire departments and police departments, for example) and to health care professionals treating exposed persons. Working through the Poison Control Center at San Francisco General Hospital, the Department of Industrial Relations has contracted to provide such services.

Consultation

Employee and employer education is another critical area of the overall occupational health program scheme. Employers must have access to expert resources helping them evaluate the hazards of a given exposure and learning how to safely control such exposures. Most states now offer free consultative services to companies requesting such services and in most states (including California) employers can get technical advice free and without fear of prosecution.

Cal/OSHA also runs an employer/employee outreach program designed to provide expertise to both labor and management groups. Recently enacted legislation in California (SB 1874) makes it mandatory to provide hazard information to all employees, making them aware of the hazards involved in handling materials with which they work.

For practicing health professionals, government-operated occupational health programs can provide valuable resources for (1) continuing education, (2) technical advice on the toxicity of a given material or clinical case management and (3) case follow-up (Cal/OSHA receives many referrals from health care providers in which we are asked to investigate and correct if necessary the work conditions of patients seen by the practitioners).

Summary

As the medical scientific community has begun to recognize the relationship between work and disease, government has responded by providing progressively more services to create a safe and healthy work environment. The primary responsibility for the provision of a healthy work environment rests with the employer. Government, however, provides education services and formulates minimum standards for the protection of workers. Although a large part of government's role is to promulgate and enforce these minimum standards, it also can provide technical toxicological and clinical occupational medicine advice.

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Key Elements of the Occupational History for the General Physician

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Taking a medical history is an art that requires skill, experience and practice. There is now increasing recognition of the importance of workplace and environmental factors in causing or aggravating common medical conditions. Because of limited training in evaluating workplace and environmental hazards, general physicians may find it difficult to target a general medical history to detect essential occupational details.

Many diseases caused by the workplace or the environment masquerade as common medical conditions that may appear resistant to standard therapy. Orthopedic difficulties, skin diseases, asthma, neuropathies, cancer and diminished hearing are all common entities with frequent exacerbations or primary causation from occupational or environmental exposures. It is difficult and sometimes impossible to obtain a detailed occupational history because an individual worker may have limited knowledge of the potential toxicities on the job. With a high index of suspicion and ready access to appropriate lines of referral, one may be able to detect or prevent important diseases. The purpose of this brief article is to outline key elements that can be added to a standard history form. It is anticipated that these additions will be useful in refining one's art and skill in detecting occupational or environmental diseases. Table 1 provides a brief guide to the key points of an occupational/environmental history.

Additions to Standard History Questions

Present Illness

Under each individual problem listed in your problem-oriented record add the following four questions:

1. *Are the symptoms associated with work? Are these symptoms improved during vacations or weekends?*
2. *Are other workers similarly affected?*
3. *Are you currently exposed to any dust, fumes or chemicals?*
4. *Was a first report of work injury filed by a physician?* (This is an extremely valuable way of identifying the specifics of an occupational injury and also identifying those physicians who evaluated the patient immediately after the suspected injury.)

Work History

1. *List in chronological order all jobs. Describe in detail the work site (diagram may be helpful). Describe a typical work day.*
2. *Was protective equipment issued; do you have knowledge of safety programs given on the job?*
3. *Is ventilation in your workplace appropriate?*
4. *Was a preemployment examination done?*
5. *Is any specialized periodic testing or medical surveillance done on current or prior jobs?*
6. *Are you aware of industrial hygiene sampling of the workplace?*
7. *List the total number of days missed on each job. List specific reasons for absenteeism.*
8. *Has a worker compensation claim ever been filed in your behalf? If so, list the specifics.*
9. *Have there been special health and safety issues presented by your labor union?*
10. *In addition to your regular work, have you ever moonlighted? List additional jobs.*

Past History

Certain occupational exposures may be subtle and require a specific response:

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TABLE 1.—*Key Points of an Occupational/Environmental History*

Present Illness (for each element of problem list)
- Symptoms related to work
- Other employees similarly affected
- Current exposure to dusts, fumes, chemicals, biologic hazards
- Prior first report of work injury

Work History
- Describe—all prior jobs
  - —typical work day
  - —change in work process
- Worksite—ventilation, medical and industrial hygiene surveillance, employment exams, protective measures
- Union health and safety
- "Moonlighting"
- Days missed work last year. Why?
- Prior worker compensation claims

Past History
- Exposure to noise, vibration, radiation, chemicals, asbestos

Environmental History
- Present and prior home and work locations
- Jobs of "significant others"
- Hazardous wastes/spills exposure
- Air pollution
- Hobbies: painting, sculpture, welding, woodworking
- Home insulation-heating
- Home and work cleaning agents
- Pesticide exposure
- Do you wear seat belts?
- Do you have firearms in home or work?

Review of Systems
- Specific emphasis: shift changes
  - boredom
  - reproductive history

1. *Have you regularly been exposed to loud noises, excessive vibration or heat?*
2. *Have you ever been exposed to asbestos?*
3. *Have you ever been exposed to radioactive chemicals or excessive radiation?*
4. *Have you been exposed to chemicals?*
5. *During military service what were your duties? Did you have any exposure to potentially toxic agents?*

Environmental Health History

There is increasing recognition of subtle problems in the environment contributing to disease:

1. *Are there any new factories located in your neighborhood?*
2. *Have you been exposed to any hazardous waste sites or toxic spills?*
3. *List jobs of spouse or significant others.*
4. *Is there commonly air pollution in your environment?*
5. *List all hobbies and recreational activities. Specifically, do you work with painting, sculpting, welding or woodworking? If so, what is the location and ventilation?*
6. *Describe the insulation and heating in your current and past living areas.*
7. *What agents are used to clean your home and workplace?*
8. *Are insecticides used in your home or environment?*
9. *Do you maintain firearms in your home or workplace?*
10. *Do you wear seat belts?*

Review of Systems

It is especially important to recognize high-risk jobs such as fire fighting, mining or forestry. Special emphasis should be placed on detecting occupational skin and lung diseases, cancer, peripheral neuropathy and liver disorders. In addition, specific questions should be asked about two special areas: working hours and reproductive history.

1. *What are your working hours? Has your job schedule required major changes of shift work that have disturbed your sleep? Are you bored on the job?*
2. Special attention to reproductive history is essential. *Record the number of miscarriages, children, stillbirths, prior pregnancies and difficulties conceiving. Have you noted any change in libido or menses?*

What to Do With a Suspicious Occupational or Environmental History

1. Be sure to obtain copies of all prior records, especially first reports of work injury.
2. Establish local lines of referral to skilled physicians and industrial hygienists with experience in this area.
3. Identify key references:
   - A useful flow diagram for a systematic approach to history taking and diagnosis of occupational diseases is provided by Goldman and Peters:
     Goldman RH, Peters JM: The occupational environmental health history. JAMA 1981 Dec 18; 246:2831-2836
   - A small but useful guide to the symptoms and signs in occupational diseases is provided in a text costing $9.95. Keep this at hand and refer to it frequently:
     Daugaard J: Symptoms and Signs in Occupational Disease; A Practical Guide. Copenhagen, Munksgaard, distributed by Year Book Medical Publishers, Inc, 1978
   - This text lists in alphabetical order common chemicals and some key references:
     Proctor N, Hughes J: Chemical Hazards of the Workplace. Philadelphia, JB Lippincott Co, 1978
   - For a useful, broad text, the following book is recommended:
     Occupational Diseases: A Guide to Their Recognition, DHEW publication No. 77-181. US Department of Health, Education, and Welfare, 1978

Book Reviews

The journal does not review all books sent by the publishers. New books received are listed in the Advertising Section. Prices quoted are those given by the publishers.

CANCER MORTALITY AND MORBIDITY STATISTICS; Japan and the World—Japanese Cancer Association GANN Monograph on Cancer Research No. 26. Edited by Mitsuo Segi, Suketami Tominaga, Kunio Aoki and Isaburo Fujimoto. ISBS, Inc., P.O. Box 1632, Beaverton, OR 97075, 1981. 274 pages, $45.00.

This is a useful compendium of cancer statistics for cancer epidemiologists and others needing cancer incidence statistics for Japan, and cancer mortality data for many countries throughout the world. Included are three papers, each with a brief discussion followed by tables or figures providing incidence or mortality data. The editors of the monograph and the authors of the papers are well-known for earlier work in this field. In particular, Professor Mitsuo Segi's graphic representations of site-specific, age-adjusted cancer death rates for international comparisons have become classics and are widely used.

The three papers in the monograph are titled "Cancer Mortality in Japan," "Cancer Incidence in Japan," and "World Cancer Mortality," respectively.

"Cancer Mortality in Japan"

The report on cancer mortality in Japan provides the following:

- The number of deaths from malignant neoplasms by site and sex and the corresponding proportionate cancer mortality (1978).
- The number of anatomical site- or system-specific cancer deaths by sex with crude and age-adjusted death rates (1935-1978).
- Age- and sex-specific cancer mortality rates at five-year intervals from 1950 to 1975 plus 1978. Time trends in age-specific death rates are plotted by calendar year and by age for birth-year cohorts. This is provided for each sex by anatomic site or system.
- Age-adjusted death rates for cancer by site and sex are given for four groupings of cities and counties in Japan in 1970 and 1975.
- Tables and figures showing standardized mortality ratios for all cancers and for specific sites and systems by prefecture of Japan for the five-year period 1973-1977.

"Cancer Incidence in Japan"

The paper on cancer incidence in Japan provides data on crude and age-adjusted annual cancer incidence rates by site and sex for each of 15 population-based cancer registries in Japan and for all registries combined. These registries provide coverage of 43 percent (47.5 million) of the population of Japan. This is supplemented by annual crude and age-adjusted cancer incidence rates by sex and cancer site for each registry (1974-1976). Estimates are also made of cancer incidence rates for the whole of Japan by projecting rates from seven of the most reliable population-based registries and with adjustment for potential underestimation or overestimation. The adjustment index was obtained from a comparison of cancer death rates from the test registry areas with that recorded for the whole of Japan. The reliability of the methodology employed in estimating national incidence figures needs further assessment.

This chapter closes with a tabulation of crude and age-adjusted annual incidence rates by sex and cancer site for the Osaka Prefecture based on the average experience over the period 1967-1976. Also provided for Osaka is a table showing the time trend in age-adjusted cancer incidence rates over the period 1963-1977.

"World Cancer Mortality"

This final paper provides cancer mortality statistics for 56 countries throughout the world. This represents an extension of the previously published material for which Professor Segi has gained renown in the past. Included are age-adjusted cancer death rates by site for the period 1950-1975; age-adjusted cancer death rates by sex and site for 1975 presented in familiar bar graph form to facilitate visual comparison among the countries for which data were available; and age-sex-specific cancer death rates by site by country for 1974, 1975 or 1976. Also given are cumulative cancer death rates by sex for certain sites in selected countries for the age interval 0 to 74 years in 1954-1955 and 1974. Other information on population counts, infant mortality and proportionate mortality from cancer is provided in the final tables of the paper.

This volume provides much information to epidemiologists or clinicians wishing to assess the magnitude of the cancer problem either in Japan or in the international community of nations. Parts of the English translation of the Japanese original are difficult to understand. Also, some of the methodology is is presented in too limited a way. Only the most cursory summary of some noteworthy observations is presented in most instances. Nevertheless, this volume is one of value and should represent a fitting testimonial to the labors of Professor Segi, word of whose death was received just as this review was begun.

It should be noted that several parallels exist between the data in this monograph and those in two recent American publications. The maps on cancer mortality in Japan are similar, on a reduced scale, to the contents of the *Atlas of Cancer Mortality for US Counties, 1950-1969* (DHEW Publication No. [NIH] 75-780). This latter volume helped identify "hot spots" for various forms of cancer in the United States. The availability of cancer incidence data for areas of Japan that maintain population-based registries is most timely, since it coincides closely with the publication in 1981 of *National Cancer Institute (NCI) Monograph 57* which provides incidence, as well as mortality data, for 1973-1977 collected by the NCI's SEER (surveillance, epidemiology and end results) program in ten parts of the United States and Puerto Rico. It is hoped that useful comparisons between the Japanese and American experience will be forthcoming.

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CONSULTANTS FOR
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Karam, John H.
Karliner, Joel S.
Kaufman, Joseph J.
Kelly, Pamela M.
Kessler, Robert
Kimbrough, R. D.
King, Haitung
Kirby, Barbara D.
Kleeman, Charles R.
Knights, Jean
Knochel, James P.
Knudson, Harlan R.
Knutson, David W.
Kolb, Felix O.
Kozin, Franklin
Kraut, Jeffrey A.
Krueger, Milton

LaForce, F. Marc
Langdell, John
Lehrer, Robert
Levy, Jay A.
Lewis, Brian J.
Lewis, Charles E.
Lief, Harold I.
Lindner, Harold H.
Linebarger, Sally
Lippe, Philipp M.
Lo, Bernard
Longmire, William J.
Luft, Harold S.
Lyman, Donald O.

Maffley, Roy A.
Manning, Phil R.
Margen, Sheldon
Margulis, Alexander R.
Martin, David W., Jr.
Marshall, Ralph K.
Massie, Barrie
Massry, Shaul G.
Matthay, Michael A.
Matychowiak, Francis A.
McAninch, Jack W.
McCarthy, Paul L.
McGowan, Jak
McKellar, Peter P.
Meakins, Jonathan L.
Meyer, Richard D.
Miller, Ronald D.
Mintz, Jim
Mobitch, Mark E.
Morady, Fred
Morrelli, Howard F.
Moser, Kenneth M.
Motulsky, Arno G.
Mulder, Donald G.
Murray, John F.
Mustacchi, Piero

Naughton, James
Nestle, Marion
Newton, Thomas H.
Nies, Alan

Orloff, Marshall
Owen, Robert L.
Owen, William F., Jr

Page, Lot B.
Pappagianis, Demosthenes
Park, Robert
Pasnau, Robert O.
Pavone, Ben
Pelletier, Lawrence L., Jr
Perkins, Woodbury
Perloff, Dorothee
Peters, Robert
Petrakis, Nicholas L.
Phillips, Theodore L.
Porte, Daniel
Pugh, Richard G.

Rackow, Eric C.
Raskin, Neil H.
Rector, Floyd C., Jr
Reich, Peter
Roberts, James C., Jr
Robinson, Scott
Roizen, Michael F.
Roof, Betty S.
Root, Richard R.
Ropper, A. H.
Rosenberg, Saul A.
Rosinski, Edwin
Rosove, Michael H.
Rosenwasser, Lanny
Rubsamen, David
Russell, Findley E.

Sadler, H. Harrison
Sagebiel, Richard
Saunders, John B. de C. M.
Schambelan, Morris
Scharschmidt, Bruce F.
Scheinman, Melvin
Scher, Maryonda
Schiller, Nelson B.
Schmidt, Joseph D.
Schrock, Theodore R.
Schroeder, Steven
Seaman, William E.
Selzer, Arthur E.
Shapiro, Bertrand J.
Sheldon, George F.
Sheline, Glenn E.
Siegel, David
Siegel, Robert C.
Simon, Harvey B.
Singleton, John
Sleisenger, Marvin H.
Smith, Charles B.
Smith, Lynwood H.
Smith, W. McPhate
Sorenson, J. Leon
Soter, Nicholas A.
Sower, Don
Sparacino, Robert
Sparling, P. Frederick
Spink, Wesley W.
Spitler, Lynn
St. Geme, Joseph, Jr
Stamatoyannopoulos, George
Stamm, Walter E.
Stauffer, John L.
Stites, Daniel P.
Stockdale, Frank E.
Stone, George C.
Stoney, Ronald J.
Storey, Veronica
Straker, Manuel
Strewler, Gordon J.
Stulbarg, Michael
Sung, Ruey J.
Sutherland, Grant R.

Tan, S. Y.
Tank, Edward S.
Taugher, Donald F.
Taylor, Philip R.
Terman, David S.
Thiele, Brian L.
Tierney, Lawrence M., Jr
Towers, Bernard
Trunkey, Donald D.

Uhley, Herman N.
Ullyot, Daniel J.
Ungerleider, J. Thomas
Utley, Joe R.

VanderLaan, W. P.
Vaughan, John H.
Ver Steeg, Donna
Volpe, Robert
Von Hoff, Daniel
Vosti, Kenneth L.

Warnock, David G.
Way, Lawrence W.
Weisfeldt, M. L.
Weiss, Joseph G.
Welby, Dorothy
Welch, Claude E.
Willenkin, Robert L.
Willett, David E.
Williams, Roger L.
Wingert, Willis
Woeber, Kenneth A.
Wood, David
Woodward, Theodore E.
Wylie, Edwin J.*

Young, Lowell S.

Zakim, David
Ziegler, Elizabeth
Ziegler, John
Zippin, Calvin
Zvaifler, Nathan J.

*Died September 2, 1982.

AUTHOR INDEX

Ament, Marvin E., Los Angeles ..... (Sep) 243
Aminoff, Michael J., San Francisco ..... (Dec) 493
Ammann, Arthur J., San Francisco ..... (Nov) 419
Avner, Dennis L., Salt Lake City ..... (Sep) 241

Bachhuber, Ray, Portland ..... (Sep) 221
Baird, Robert A., Orange, CA ..... (Jul) 80
Bankhurst, Arthur, Albuquerque ..... (Nov) 448
Baxi, Sunita C., La Jolla, CA ..... (Nov) 429
Bayley, Corrine, Orange, CA ..... (Jul) 83
Becker, Charles E., San Francisco .....
(Oct) 282, 320, 346, (Dec) 478, 493, 581
Beeson, Paul B., Seattle ..... (Sep) 239
Berek, Jonathan S., Los Angeles ..... (Oct) 273
Birnbaum, Neal S., San Francisco ..... (Jul) 78
Blake, Paul A., Atlanta ..... (Nov) 365
Bopp, Cheryl A., Atlanta ..... (Nov) 365
Boyle, Joseph F., Los Angeles ..... (Nov) 436
Brant-Zawadzki, Michael, San Francisco ..... (Jul) 65
Bruce, Robert A., Seattle ..... (Jul) 76
Buist, A. Sonia, Portland ..... (Oct) 294
Burkart, John A., Salt Lake City ..... (Nov) 440

Callaham, Michael, San Francisco ..... (Nov) 425
Carr, Kenneth W., San Diego ..... (Sep) 245
Casciato, Dennis A., Los Angeles ..... (Nov) 439
Cassel, Christine K., Portland ..... (Nov) 437
Chan, Michael Kwok L., San Francisco ..... (Aug) 132
Chang, Albert, Los Angeles ..... (Aug) 162
Chu, Joseph, Seattle ..... (Jul) 13, (Oct) 338
Coleman, Arthur H., San Francisco ..... (Jul) 76
Conte, Felix A., San Francisco ..... (Jul) 61
Conti, Sebastian, Carmichael, CA ..... (Jul) 81
Crooks, Lawrence E., San Francisco ..... (Oct) 290
Cullen, Bruce F., Irvine, CA ..... (Jul) 67
Cummings, Steven R., San Francisco ..... (Nov) 443
Cunningham, Thomas M., San Francisco ..... (Sep) 186
Cushing, Alice H., Albuquerque ..... (Nov) 448
Cutting, Hunter O., Oakland, CA ..... (Oct) 325

Dailey, George E. III, La Jolla, CA ..... (Nov) 429
Davis, Joseph H., Palo Alto, CA ..... (Jul) 79
Davis, Peter L., San Francisco ..... (Oct) 290
DeBusk, Robert Frank, Stanford, CA ..... (Dec) 515
Deedwania, Prakash C., Fresno, CA ..... (Jul) 24
Dellinger, Patchen E., Seattle ..... (Sep) 181
Dennis, Charles Andrew, Stanford, CA ..... (Dec) 515
Depner, Thomas A., Sacramento, CA ..... (Oct) 322
Dobie, Robert A., Seattle ..... (Dec) 499
Driscoll, Charles E., Iowa City ..... (Nov) 379

Edwards, William A., Seattle ..... (Sep) 181
Eisenberg, Harvey, Irvine, CA ..... (Jul) 67
Elias, Alan N., Irvine, CA ..... (Jul) 67
Elliot, Diane L., Portland ..... (Oct) 351
Embury, Stephen H., San Francisco ..... (Oct) 325

Finkle, Alex L., San Francisco ..... (Aug) 95
Fisher, Nancy L., Seattle ..... (Jul) 32
Fitchen, John H., Portland ..... (Sep) 221
Fitzgerald, Faith T., Davis, CA ..... (Aug) 169
Foliart, Donna, San Francisco ..... (Oct) 346
Forquer, Brian D., Los Angeles ..... (Nov) 370
Fox, E. R. W., Coeur d'Alene, ID ... (Oct) 359, (Nov) 441
Frank, Hugh A., San Diego ..... (Sep) 252
Frost, Floyd, Olympia, WA .(Sep) 250, (Oct) 339, (Nov) 436

Gabriel, Juan B., New York City ..... (Nov) 435
Garabrant, David H., Los Angeles ..... (Dec) 555
Glazener, Frederick S., Stanford, CA ..... (Oct) 328
Glover, Thomas W., Tempe, AZ ..... (Oct) 278
Golden, Jeffrey, San Francisco ..... (Nov) 400
Golden, Michael P., Irvine, CA ..... (Jul) 67
Goldenring, John M., Los Angeles ..... (Sep) 251
Goldman, Marvin, Davis, CA ..... (Dec) 540
Gregoratos, Gabriel, San Diego ..... (Sep) 245
Grisolia, J. S., La Jolla, CA ..... (Nov) 438
Grossman, Moses, San Francisco ..... (Jul) 60
Grumbach, Melvin M., San Francisco ..... (Jul) 61

Hacker, Neville F., Los Angeles ..... (Oct) 273
Hall, Judith G., Vancouver, BC ..... (Jul) 32
Haller, John S., Jr., Long Beach, CA ..... (Sep) 258
Harty-Golder, Barbara, Portland ..... (Sep) 221
Haynes, Bruce, Torrance, CA ..... (Aug) 139
Head, Richard M., Fortuna, CA ..... (Oct) 338
Healey, Kathy, San Francisco ..... (Oct) 282
Healy, Francis A., Burlingame, CA ..... (Jul) 83
Healy, James L., Albuquerque ..... (Nov) 448
Hearne, Christopher Baillie, Salt Lake City ..... (Nov) 431
Hecht, Frederick, Tempe, AZ ..... (Oct) 278
Hendrickson, Charles S., San Francisco ..... (Aug) 132
Heyman, Melvin B., San Francisco ..... (Sep) 243
Hill, Richard, Fairfield, CA ..... (Aug) 140
Holbrook, John H., Salt Lake City ..... (Aug) 125
Holman, Bob, Seattle ..... (Oct) 339
Hooper, Kim, Berkeley, CA ..... (Dec) 560
Hossack, Kenneth F., Seattle ..... (Jul) 76
Hughes, James P., Oakland, CA ..... (Dec) 498
Hunt, Thomas K., San Francisco ..... (Aug) 128

Jackson, Shirley, San Francisco ..... (Aug) 95
Johnson, Allen D., San Diego ..... (Sep) 245
Jones, Phillip, Bellingham, WA ..... (Nov) 436
Jung, Ralph C., Los Angeles ..... (Aug) 138

Kaiser-McCaw, Barbara, Tempe, AZ ..... (Oct) 278
Kane, Joseph A., Portland ..... (Oct) 351
Kaufman, Jeffrey L., Piscataway, NJ ..... (Nov) 437
Kaufman, Leon, San Francisco ..... (Oct) 290
Kerndt, Peter R., San Francisco ..... (Nov) 379
Khajawall, Ali M., Norwalk, CA ..... (Aug) 166
Kobayashi, John, Seattle ..... (Nov) 436
Koller, Richard, Portland ..... (Oct) 335
Kondlapoodi, Preetham, New York City .....
(Jul) 77, (Aug) 138, (Nov) 435
Kornfield, Harrison J., Sunnyvale, CA ..... (Oct) 338
Krishnamurthy, Gerbail T., Portland ..... (Aug) 87
Kunin, Calvin M., Columbus, OH ..... (Sep) 237

LaDou, Joseph, Sunnyvale, CA ..... (Dec) 525
Lagasse, Leo D., Los Angeles ..... (Oct) 273
Landrigan, Philip J., Cincinnati ..... (Dec) 531
Langou, Rene A., New Haven, CT ..... (Nov) 422
Larsen, Robert, San Francisco ..... (Sep) 265
Lasnover, Alan L., Cupertino, CA ..... (Jul) 77
Leskowitz, Rick, Fresno, CA ..... (Nov) 438
Levy, Esther, Los Angeles ..... (Aug) 162
Lewis, Robert A., Boston ..... (Sep) 234
Liebhaber, Stephen A., San Francisco ..... (Oct) 325
Linthicum, Fred H., Jr., Los Angeles ..... (Nov) 370
Linz, Douglas H., Portland ..... (Oct) 351
Lipsett, James A., Duarte, CA ..... (Nov) 375
Lockey, James E., Salt Lake City ..... (Dec) 548
Locksley, Richard M., Seattle ..... (Jul) 45
Longstreth, W. T., Jr., Seattle ..... (Aug) 134
Lotti, Marcello, San Francisco ..... (Dec) 493
Loxterkamp, David A., Iowa City ..... (Nov) 379

Maibach, Howard I., San Francisco ..... (Dec) 486
Mako, Mary, Chicago ..... (Jul) 67
Margulis, Alexander R., San Francisco ..... (Oct) 290

Mark, James B. D., Stanford, CA ... (Nov) 435
Marquardt, Diana L., San Diego ... (Sep) 195
Mathias, C. G. Toby, San Francisco ... (Dec) 486
McConnell, Thomas S., Albuquerque ... (Nov) 448
McIlvenna, Patricia A., Albuquerque ... (Nov) 448
McPhee, Stephen J., San Francisco ... (Aug) 145, (Sep) 253
Mecikalski, Mark B., Salt Lake City ... (Oct) 322
Merimee, Thomas J., Gainesville, FL ... (Nov) 418
Meshkinpour, Hooshang, Orange, CA ... (Aug) 130
Miller, Don R., Irvine, CA ... (Jul) 67
Miller, Hillary G., Atlanta ... (Nov) 365
Minkowski, William L., Los Angeles ... (Nov) 451
Moore, Byron C., Tempe, AZ ... (Oct) 278
Morse, Linda, San Francisco ... (Oct) 346
Moser, Kenneth M., San Diego ... (Jul) 81
Myers, Lois P., San Francisco ... (Aug) 145

Naughton, James L., San Francisco ... (Oct) 302, (Nov) 379
Nierenberg, David W., Hanover, NH ... (Oct) 328
Nishimura, Robert N., Sepulveda, CA ... (Oct) 335

Olson, Kent R., San Francisco ... (Oct) 282
Oreskovich, Michael R., Seattle ... (Sep) 181
Osibin, Willard S., Templeton, CA ... (Jul) 83

Papadakis, Maxine A., San Francisco ... (Aug) 141
Paterno, Victoria I., Los Angeles ... (Sep) 243
Patmas, Michael A., Reno, NV ... (Jul) 80
Perkins-Jones, Kathy, Seattle ... (Oct) 339
Peters, John M., Los Angeles ... (Dec) 555
Pezner, Richard D., Duarte, CA ... (Nov) 375
Pierson, David J., Seattle ... (Aug) 134
Pohost, Gerald M., Boston ... (Oct) 319
Polissar, Lincoln, Seattle ... (Jul) 13
Polito, Gregory, Whittier, CA ... (Jul) 82
Pond, Susan M., San Francisco ... (Oct) 282, (Dec) 506
Pont, Allan, San Francisco ... (Oct) 331
Porter, Bruce W., Tucson ... (Nov) 365

Rappaport, Stephen M., Berkeley, CA ... (Dec) 572
Reed, Susan D., Seattle ... (Jul) 32
Rikkers, Layton F., Salt Lake City ... (Sep) 241
Robinson, Alfred G., Camarillo, CA ... (Sep) 251
Rom, William N., Salt Lake City ... (Dec) 548
Romansky, Stephen G., Irvine, CA ... (Jul) 67
Rubenstein, Arthur H., Chicago ... (Jul) 67

Sahn, Steven A., Denver ... (Aug) 99
Sanazaro, Paul J., Berkeley, CA ... (Aug) 127
Sapico, Francisco L., Downey, CA ... (Jul) 18
Sarma, Radha J., Los Angeles ... (Jul) 18
Schechter, Gisela, San Francisco ... (Jul) 65
Schoolman, Harold M., Bethesda, MD ... (Nov) 460
Schroeder, Steven A., San Francisco ... (Aug) 145
Seward, James, San Francisco ... (Oct) 282
Shapiro, Edward, Los Angeles ... (Aug) 139
Shapiro, Marvin J., Encino, CA ... (Sep) 251
Sheldon, Gerard P., San Francisco ... (Aug) 140
Sheppard, Dean, San Francisco ... (Dec) 480
Shoemaker-Nawas, Phyllis, Seattle ... (Nov) 436
Shulman, Irving, Los Angeles ... (Jul) 79
Silver, Diane S., Napa, CA ... (Sep) 191
Simonowitz, David A., Seattle ... (Sep) 181
Simpson, George M., Los Angeles ... (Aug) 166
Singh, Bramah N., Los Angeles ... (Jul) 62
Skipper, Betty J., Albuquerque ... (Nov) 448
Smith, James B., Seattle ... (Oct) 339
Smith, Lloyd H., Jr., San Francisco ... (Oct) 317
Soman, Michael, Sacramento, CA ... (Jul) 1
Spear, Robert C., Berkeley, CA ... (Dec) 572
Spratt, Daniel I., San Jose, CA ... (Oct) 331
Sramek, John J., Jr., Norwalk, CA ... (Aug) 166
Stamm, Walter E., Seattle ... (Sep) 213
Starzyk, Patricia, Olympia, WA ... (Sep) 250
Stettner, Joel A., Oakland, CA ... (Nov) 442
Stopo, John D., San Francisco ... (Aug) 109
Stothert, Joseph C., Seattle ... (Sep) 181
Sybert, Virginia P., Seattle ... (Jul) 32

Tamimi, Hisham K., Seattle ... (Jul) 13, (Oct) 338
Tanner, Sterling M., Irvine, CA ... (Jul) 67
Taylor, David N., Atlanta ... (Nov) 365
Taylor, Kathleen E., San Francisco ... (Aug) 132
Terplan, Martin, San Francisco ... (Sep) 250
Tierney, Lawrence M., Jr., San Francisco ... (Aug) 169
Tisi, Gennaro M., La Jolla, CA ... (Aug) 124
Tong, Theodore G., San Francisco ... (Oct) 320, 346
Trimble, George X., Kansas City, MO ... (Jul) 78
Tupper, C. John, Davis, CA ... (Nov) 467

Valenta, Lubomir J., Irvine, CA ... (Jul) 67
Vaughn, Leroy W., Inglewood, CA ... (Sep) 269
Vaziri, N. D., Orange, CA ... (Aug) 130

Wade, Richard, Berkeley, CA ... (Dec) 577
Wagner, Gail M., Oakland, CA ... (Oct) 325
Wanetick, Lawrence H., Fairfield, CA ... (Aug) 140
Wasserman, Stephen I., San Diego ... (Sep) 195
Watts, Malcolm S. M., San Francisco ...
(Jul) 83, (Oct) 317, (Dec) 477
Werner, Mindy, San Francisco ... (Jul) 83
Werner, S. Benson, Berkeley, CA ... (Nov) 468
West, Hans C., Salt Lake City ... (Sep) 241
White, Laurens P., San Francisco ... (Jul) 83
White, Richard H., Sacramento, CA ... (Oct) 340
Whorton, M. Donald, Berkeley, CA ... (Dec) 521
Wiederholt, W. C., La Jolla, CA ... (Nov) 438
Williams, Cynthia A., Phoenix ... (Nov) 365
Williamson, Roger A., Seattle ... (Jul) 32
Wolfsy, Constance B., San Francisco ... (Jul) 65
Woo, Olga F., San Francisco ... (Oct) 282
Wright, William E., Los Angeles ... (Dec) 555

Yager, Janice W., Berkeley, CA ... (Dec) 572

Zacherle, Barry J., Napa, CA ... (Sep) 191
Zawada, Edward T., Jr., Richmond, VA ... (Nov) 431

IN MEMORIAM

California Medical Association:

Auvil, Raymond George, Apr 21, 1982 ... (Nov) 476
Baker, Thomas Hart, Jul 4, 1982 ... (Sep) 271
Balcer, Edwin A., May 13, 1982 ... (Nov) 476
Beumer, Oliver C., Sep 17, 1982 ... (Nov) 476
Brockbank, Mark J., Aug 17, 1982 ... (Nov) 476
Chambers, Jack, Jun 2, 1982 ... (Nov) 476
Coates, Gaines L., Mar 25, 1982 ... (Aug) 176
Cox, George W., May 17, 1982 ... (Nov) 476
Crawford, Joseph William, Apr 21, 1982 ... (Sep) 271
Crow, Lloyd B., Aug 18, 1982 ... (Oct) 363
Cuneo, Joseph C., Apr 6, 1982 ... (Nov) 476
Curry, William H., Mar 7, 1982 ... (Aug) 176
Damron, Milton H., Mar 26, 1982 ... (Aug) 176
Davis, Burt L., Apr 8, 1982 ... (Aug) 176
Dedinsky, John J., Jun 19, 1982 ... (Oct) 363
Dole, Kenneth L., Apr 8, 1982 ... (Nov) 476
Donoghue, Charles K., Jul 15, 1982 ... (Nov) 476
Ehret, Edward E., Jun 27, 1982 ... (Nov) 476
Elconin, Ann Frank, Apr 24, 1982 ... (Aug) 176
Eldredge, Horace S., Jul 19, 1982 ... (Oct) 363
Fagin, Paul, Dec 3, 1981 ... (Sep) 271
Fishback, Dora K., Aug 16, 1982 ... (Oct) 363
Fleisher, Arthur J., Jul 2, 1982 ... (Oct) 363
Gallagher, Henry F., Jan 2, 1982 ... (Sep) 271
Geyman, Milton J., May 12, 1982 ... (Sep) 271
Groezinger, Catharine H., Jul 12, 1982 ... (Sep) 271
Helbling, Franklin K., Feb 5, 1982 ... (Sep) 271

Heneks, William Eugene, Mar 20, 1982 .....(Aug) 176
Hershey, Christian J., Oct 20, 1981 .....(Nov) 476
Higgins, Laurie W., Apr 15, 1982 .....(Aug) 176
Hope, Fritz, Apr 1, 1982 .....(Aug) 176
Hunter, Derek Walter, Mar 16, 1982 .....(Sep) 271
Kaplan, Harry E., Jun 7, 1982 .....(Nov) 476
Kelso, George Frederick, May 5, 1982 .....(Sep) 271
Khoury, Elias F., Jul 2, 1982 .....(Oct) 363
Kiyasu, Kunisada, Jul 23, 1982 .....(Oct) 363
Kutzmann, Adolph A., Jan 21, 1982 .....(Nov) 476
Leon, Tim Daniel, Aug 1982 .....(Oct) 363
Luttgens, William F., May 27, 1982 .....(Aug) 176
Magrath, William A. S., Jan 27, 1982 .....(Sep) 271
Mahon, Edmund J., Jul 6, 1982 .....(Oct) 363
McNie, Allan B., May 10, 1982 .....(Aug) 176
Mehlin, G. Burch, May 7, 1982 .....(Aug) 176
Melody, George F., Apr 7, 1982 .....(Aug) 176
Merchant, Robert F., Jun 23, 1982 .....(Oct) 363
Nelson, Leroy J., Mar 31, 1982 .....(Aug) 176
Neslen, George Quayle, Sr., May 15, 1982 .....(Sep) 271
Patrick, John E., May 17, 1982 .....(Sep) 271
Patterson, John A., Apr 5, 1982 .....(Aug) 176
Pendergrass, Clayton I., Jul 6, 1982 .....(Oct) 363
Penn, Harry S., Nov 19, 1981 .....(Sep) 271
Percy, Archibald, May 28, 1982 .....(Sep) 271
Pinder, Donald E., Jul 2, 1982 .....(Oct) 363
Poliak, Percy P., Feb 10, 1982 .....(Sep) 271
Pollack, Seymour, Apr 8, 1982 .....(Aug) 176
Polland, W. Scott, Apr 3, 1982 .....(Aug) 176
Porter, Clarence Chipley, May 15, 1982 .....(Aug) 176
Quinn, William F., May 15, 1982 .....(Aug) 176
Rapaport, Walter, Mar 19, 1982 .....(Aug) 176
Reid, Robert Huestis, Jun 9, 1982 .....(Aug) 177
Renger, J. John, Oct 10, 1981 .....(Sep) 271
Risser, Joseph C., Sr., Mar 11, 1982 .....(Aug) 177
Rixford, Emmet L., Jr., Jul 31, 1982 .....(Oct) 363
Rogers, William E., Apr 10, 1982 .....(Aug) 177
Rutherford, Miriam H., Mar 23, 1982 .....(Aug) 177
Sandie, Joseph, Feb 22, 1982 .....(Aug) 177
Still, Richard Mathias, Apr 22, 1982 .....(Aug) 177
Stimson, Clement A., Jul 30, 1982 .....(Oct) 363
Stirrett, Robert L., Jan 28, 1982 .....(Sep) 271
Weinstein, Hyman William, Apr 14, 1982 .....(Aug) 177
West, Francis E., Aug 24, 1982 .....(Oct) 363
Whitson, Robert O., Jan 27, 1982 .....(Sep) 271
Wylie, Edwin J., Sep 2, 1982 .....(Oct) 363
Young, Henry Marcus, Aug 5, 1982 .....(Oct) 363
Zwerling, Henry B., Jan 15, 1982 .....(Sep) 271

Idaho Medical Association:

Bond, S. Wallace, Mar 4, 1982 .....(Oct) 363
Budge, Alfred H., Feb 19, 1982 .....(Oct) 364
Davis, George E., 1982 .....(Oct) 364
Florentz, Theodore R., Feb 5, 1982 .....(Oct) 364
Gallivan, Edward L., Mar 29, 1982 .....(Nov) 476
Hahn, Robert F., Aug 13, 1982 .....(Oct) 364
Jensen, Robert H., Apr 9, 1982 .....(Oct) 364
Johnson, Howard E., Jan 1, 1982 .....(Oct) 364
Mack, James F., Dec 6, 1981 .....(Oct) 364
McWilliams, Charles R., Sep 18, 1982 .....(Nov) 476
Morris, Judson B., Jan 1, 1982 .....(Oct) 364
Moseley, H. Don, 1982 .....(Oct) 364
Starck, Jimmie C., Sep 25, 1982 .....(Nov) 476

New Mexico Medical Society:

Brown, Warren T., May 10, 1982 .....(Aug) 177
Martin, John W., Apr 21, 1982 .....(Aug) 177
McCrory, James L., Jun 29, 1982 .....(Oct) 364
Weston, James T., May 10, 1982 .....(Aug) 177

Utah State Medical Association:

Crockett, Kenneth Adams, Apr 6, 1982 .....(Sep) 272
Eddington, Elmo, Aug 23, 1982 .....(Nov) 476
Prestwich, James Sheldon, Jun 26, 1982 .....(Oct) 364
Reichmann, Wilford J., Jun 8, 1982 .....(Sep) 272
Webster, James Weldon, Aug 13, 1982 .....(Nov) 476
Winget, Frank J., Mar 30, 1982 .....(Sep) 272
Wright, John K., Jun 19, 1982 .....(Oct) 364

Washington State Medical Association:

Bailey, Richard J., Aug 13, 1981 .....(Sep) 272
Gorton, Samuel H., Apr 29, 1982 .....(Sep) 272
Heilbrunn, Gert, May 8, 1982 .....(Oct) 364
Hildebrand, Carl H., Jun 13, 1982 .....(Sep) 272
Hill, Robert M., Mar 3, 1982 .....(Sep) 272
Jordan, Richard, Apr 26, 1982 .....(Aug) 177
Judy, Harriet E., Sep 11, 1981 .....(Sep) 272
Kindschi, Jean Douglas, Dec 24, 1981 .....(Sep) 272
Kohl, Gerald C., Jan 17, 1981 .....(Sep) 272
Kraabel, Donovan O., Dec 17, 1981 .....(Aug) 177
Lee, Albert Francis, Mar 1, 1982 .....(Aug) 177
Lee, Jack W., Mar 13, 1981 .....(Sep) 272
Leonard, John Michael, Apr 3, 1982 .....(Aug) 177
Manning, James Howard, Feb 17, 1982 .....(Aug) 177
Mattes, J. Joseph, Apr 29, 1982 .....(Sep) 272
McLemore, Ira O., Mar 10, 1982 .....(Aug) 177
Pelley, John W., Nov 12, 1981 .....(Sep) 272
Pinto, Sherman S., Apr 21, 1982 .....(Sep) 272
Reberger, Charles C., Feb 9, 1982 .....(Sep) 272
Rowberg, Raymond G., Oct 23, 1981 .....(Sep) 272
Samman, Howard David, Jan 30, 1982 .....(Aug) 177
Struse, William P., Dec 21, 1981 .....(Sep) 272
Sutton, Robert C., Dec 4, 1981 .....(Aug) 177
Suzuki, M. Paul, Jun 1, 1982 .....(Sep) 272
Waterman, John H., May 1982 .....(Oct) 364
Weitz, Henry E., Mar 11, 1982 .....(Aug) 177
Willard, Don G., Apr 10, 1981 .....(Sep) 272
Yarbro, Jesse L., Apr 11, 1982 .....(Oct) 364

Wyoming Medical Society:

Hambly, Alvin S., Jul 17, 1982 .....(Oct) 364

SUBJECT INDEX

A

Acronyms in Medical Papers (Correspondence), Alfred G. Robinson .....(Sep) 251
Acquired Immune Dysfunction in Homosexual Men (Editorial), Arthur J. Ammann .....(Nov) 419
Acute Arthritis in the Elderly (Correspondence), Neal S. Birnbaum .....(Jul) 78
Acute Cholecystitis: The Diagnostic Role for Current Imaging Tests, Gerbail T. Krishnamurthy .....(Aug) 87
Correspondence, Jeffrey L. Kaufman .....(Nov) 437
Adenovirus Infection, see *Association of Myoglobinuria*
Adoptees, see *Birth Parents*
Admission Criteria for Tricyclic Antidepressant Ingestion, Michael Callaham .....(Nov) 425
Editorial, Rene A. Langou .....(Nov) 422
Advances in Clinical Medicine, see *Epitomes*
Allergic Diseases, see *Mast Cell*
Allergy, see *Epitomes*
AMA and a National Health Policy, The (Editorial)(Aug) 126
Correspondence, Joseph F. Boyle .....(Nov) 436
Amanita phalloides-Type Mushroom Poisoning, Kent R. Olson, Susan M. Pond, James Seward, Kathy Healey, Olga F. Woo, Charles E. Becker .....(Oct) 282
Editorial, Charles E. Becker, Theodore G. Tong .(Oct) 320
Aminophylline-induced Exfoliative Dermatitis: Cause and Implications, David W. Nierenberg, Frederick S. Glazener ...(Oct) 328
Anatomy, Physiology and Pathology of Biomedical Information, Harold M. Schoolman .....(Nov) 460
Anemia, see *Evaluation of*

[Anemia] Hemoglobin-H Disease, see *Hematologic Improvement*
Anergy in High-Risk Surgical Patients: The Role of Parenteral Nutrition, David A. Simonowitz, E. Patchen Dellinger, Michael R. Oreskovich, Joseph C. Stothert, William A. Edwards .....(Sep) 181
Another Indication for Coronary Bypass (Correspondence), Robert A. Bruce, Kenneth F. Hossack ...(Jul) 76
Antidepressant Ingestion, see *Admission Criteria*
Are Volcanoes Hazardous to Your Health? What Have We Learned From Mount St Helens?, see *Specialty Conferences*
Armaments, see *Nuclear*
Arsenic, see *Occupational and Community Exposures*
Arthritis, see *Acute*
Arthritis, see *Rheumatoid*
Arthritis, see *Viral/Bacterial Vaccines*
Arthritis Associated With Carcinoma, see *Poly-*

Articles To Read in Other Journals .....(Jul) 17, 23, 44
[Asbestos Exposure], see *Diffuse Malignant Mesothelioma*
Ascaris Infection in Washington State (Correspondence), Phyllis Shoemaker-Nawas, Floyd Frost, John Kobayashi, Phillip Jones .....(Nov) 436
Ascites, see *Bilious*
Ash Babies Never Came, The [Mount St Helens] (Correspondence), Patricia Starzyk, Floyd Frost .....(Sep) 250
Association of Myoglobinuria With Adenovirus Infection, Hooshang Meshkinpour, N. D. Vaziri .....(Aug) 130
Asthma, see *Occupational*

B

Babies [Mount St Helens], see *Ash*
Bacteria, see *Infective Endocarditis Due To*
Bacterial Vaccines, see *Viral*
[Bartter's Syndrome], see *Clinical Features of Covert Diuretic Use*
Bedside Sherlock Holmes, The (Information), Faith T. Fitzgerald, Lawrence M. Tierney .....(Aug) 169
Correspondence, J. S. Grisolia, W. C. Wiederholt .(Nov) 438
Correspondence, Joel A. Stettner .....(Nov) 442
Beta Cell in Management of Insulinoma, see *Value of Artificial*
(BEVA) Biological Effects of Volcanic Ash Study Center, see *Specialty Conferences*
Bibliography, see *Costs and Risks of Medical Care*
Bilious Ascites Simulating Tuberculous Peritonitis, Dennis L. Avner, Hans C. West, Layton F. Rikkers(Sep) 241
Biofeedback, see *Reconsideration of*
Biological Effects of Volcanic Ash (BEVA) Study Center, The Oregon Health Sciences University, see *Specialty Conferences*
Biomedical Information, see *Anatomy, Physiology*
Birth Parents, Adoptive Parents and Adoptees (Correspondence), Joseph H. Davis .....(Jul) 79
Bladder, see *In Defense of the*
Bleeding After Liver Biopsy (Correspondence), Preetham Kondlapoodi .....(Jul) 77
Blindness in Pregnancy, see *Isolated Cortical*
Block, see *Transient Bifascicular*
Blockers, see *Calcium Channel*
Bone Densitometry (Medical Practice Questions) .(Nov) 459

Book Reviews:
Abdominal Radiology, *McCort et al* .....(Oct) 361
Andrews' Diseases of the Skin—7th Ed., *Domonkos et al* .....(Oct) 362
Annual Review of Neuroscience—Vol 5, *Cowan et al* .....(Nov) 473
Annual Review of Nutrition—Vol 1, *Darby et al* ..(Nov) 472
Bone Metastasis, *Weiss & Gilbert* .....(Oct) 361
Cancer Mortality and Morbidity Statistics: Japan and the World, *Segi et al* .....(Dec) 583
Cancer of the Head and Neck, *Suen & Myers* .....(Oct) 362
Coping in Medical School, *Virshup* .....(Nov) 475
Current Pediatric Diagnosis & Treatment—7th Ed., *Kempe et al* .....(Nov) 471
Douglas-Stromme Operative Obstetrics—4th Ed., *Quilligan & Zuspan* .....(Nov) 474
Drug Treatment—Principles and Practice of Clinical Pharmacology and Therapeutics, 2nd Ed., *Avery* ....(Aug) 180
Elbow, The *Wadsworth* .....(Nov) 471
Fetal Heart Monitoring, *Freeman & Garite* .....(Aug) 180
General Urology—10th Ed., *Smith* .....(Oct) 362
International Textbook of Medicine—Vol 1, see *Pathophysiology*
Obstetric Ultrasound: Applications and Principles, *Van Bergen* .....(Oct) 361
Office Gynecology, 2nd Ed., *Glass* .....(Nov) 471
Paediatric Cardiology—Vol 4, *Godman* .....(Nov) 472
Pathophysiology: The Biological Principles of Disease—Vol I of *International Textbook of Medicine, Smith & Thier* .....(Nov) 475
Physician's Handbook—20th Ed., *Krupp et al* ....(Nov) 473
Progress in Perinatal Neurology—Vol 1, *Korobkin & Guilleminault* .....(Oct) 362
Recent Advances in Occupational Health, *McDonald* .....(Dec) 524
So You Want To Be a Doctor?, *Bluestone* .....(Nov) 474
Ultrastructural Appearances of Tumours—A Diagnostic Atlas, *Henderson & Papadimitrion* .....(Nov) 471
Willis's Oxford Casebook (1650-52), *Dewhurst* ..(Nov) 473

Breast Carcinoma, see *Polyarthritis*
Buerger's Disease, see *Pulmonary Embolism*

C

Cadmium, see *Occupational and Community Exposures*
Calcium Channel Blockers (Medical Progress), Prakash C. Deedwania .....(Jul) 24
Editorial, Bramah N. Singh .....(Jul) 62
California Model for Treatment of the Impaired Physician (Information), Robert Larsen .....(Sep) 265
California, Perinatal Services, see *Infant Passenger Safety*
Campylobacter, see *Waterborne Transmission*
Campylobacter Colitis: A Cause of Chronic Diarrhea in Children, Melvin B. Heyman, Victoria I. Paterno, Marvin E. Ament .....(Sep) 243
Campylobacter Enteritis: A Large Outbreak Traced to Commercial Raw Milk, David N. Taylor, Bruce W. Porter, Cynthia A. Williams, Hillary G. Miller, Cheryl A. Bopp, Paul A. Blake .....(Nov) 365
Cancer, see *Human Tumor Stem Cell*
Cancer, see *Occupational Epidemiology*
Cancer, see *Tobacco and*
Cancer, Cervical, see *Quality of Care of Women With*
Carcinoma, Breast, see *Polyarthritis*
Cardiac Disease, see *Occupational Work Evaluation*
[Cardiovascular Physiologic Processes], see *Calcium Channel Blockers*
Cardiovascular Therapeutics, see *Calcium Channel Blockers*
Care for Terminally Ill Patients: Commentary From Coeur d'Alene, E. R. W. Fox .....(Oct) 359
Cerebral Hemorrhage, see *Survival After Intra-*
Cervical Cancer, see *Quality of Care of Women*
Challenge Food Testing for Respiratory Disorders (Medical Practice Questions) .....(Sep) 194
Challenge Food Testing for Rheumatoid Arthritis (Medical Practice Questions) .....(Oct) 277
Cheating Beyond Medical School (Correspondence), Alan L. Lasnover .....(Jul) 77
Chest Trauma, Blunt, see *Transient Bifascicular Block*
Children, see *Diagnostic Workup of Febrile*
Children, see *Middle Ear Effusion*
Children, Chronic Diarrhea in, see *Campylobacter* Colitis
Cholecystitis, see *Acute*

Cigarette Smoking, see *Kicking the Habit*
Claims Data, see *Physician Behavior Modification*
Clinical Aspects of Infectious Mononucleosis (Topics in Primary Care Medicine), Maxine A. Papadakis .(Aug) 141
Clinical Features of Covert Diuretic Use, Daniel I. Spratt, Allan Pont .....(Oct) 331
Clinical Medicine, Advances, see *Epitomes*

Clinicopathologic Conference:

Rash and Eosinophilia in a 23-Year-Old-Man, Discussants: Ray Bachhuber, John H. Fitchen, Barbara Harty-Golder .....(Sep) 221
Editorial, Paul B. Beeson .....(Sep) 239

[CMA Committee on Evolving Trends in Society Affecting Life, Report of], see *Ethical Problems*
Cochlear Implants for Deafness (Medical Practice Questions) .....(Nov) 374
[Codeine and Glutethimide], see *'Loads' Alert*
Colitis, see *Campylobacter*
[Comatose States] Insulinoma, see *Value of Artificial Beta Cell in Management*

Commentary:

Commentary from Coeur d'Alene: Care for Terminally Ill Patients, E. R. W. Fox .....(Oct) 359

Comments on Ethical Protocol (Correspondence):
Marvin J. Shapiro .....(Sep) 251
John M. Goldenring .....(Sep) 251
Hugh A. Frank .....(Sep) 252
[Committee on Evolving Trends in Society Report], see *Medical Ethics*
[Computerized Tomography], see *CT Evidence*
[Computers], see *High Rock, High Tech*
Coronary Bypass, see *Another Indication for*

Correspondence:

Acronyms in Medical Papers, Alfred G. Robinson .(Sep) 251
Acute Arthritis in the Elderly, Neal S. Birnbaum ..(Jul) 78
AMA and a National Health Policy, Joseph F. Boyle .....(Nov) 436
Another Indication for Coronary Bypass, Robert A. Bruce, Kenneth F. Hossack .....(Jul) 76
Ascaris Infection in Washington State, Phyllis Shoemaker-Nawas, Floyd Frost, John Kobayashi, Phillip Jones .....(Nov) 436
Ash Babies Never Came [Mount St Helens], Patricia Starzyk, Floyd Frost .....(Sep) 250
Birth Parents, Adoptive Parents and Adoptees, Joseph H. Davis .....(Jul) 79
Bleeding After Liver Biopsy, Preetham Kondlapoodi (Jul) 77
Cheating Beyond Medical School, Alan L. Lasnover (Jul) 77
Comments on Ethical Protocol:
Marvin J. Shapiro .....(Sep) 251
John M. Goldenring .....(Sep) 251
Hugh A. Frank .....(Sep) 252
Diagnosis of Testicular Torsion, Bruce Haynes ....(Aug) 139
Differential Diagnosis of Pleural Effusions:
Preetham Kondlapoodi, Juan B. Gabriel .....(Nov) 435
James B. D. Mark .....(Nov) 435
Distinction in Terminology, Joel A. Stettner .....(Nov) 442
Heparin-Induced Thrombocytopenia:
Robert A. Baird .....(Jul) 80
Sebastian Conti .....(Jul) 81
Reply, Kenneth M. Moser .....(Jul) 81
High Rock, High Tech and Karl Marx, E. R. W. Fox .....(Nov) 441
Holistic Medicine: Advances and Shortcomings, Edward Shapiro .....(Aug) 139
How Much Testing Is Needed?, Ralph C. Jung ...(Aug) 138
Leukemia in Hospital Patients With Occupational Exposure to the Sawmill Industry, John A. Burkart ..(Nov) 440
Needle in the Foot, Lawrence H. Wanetick, Richard Hill .....(Aug) 140
Nuclear Armaments:
Christine K. Cassel .....(Nov) 437
Rick Leskowitz .....(Nov) 438
'Opening Up' the Health Care System, Gregory E. Polito .....(Jul) 82
Pacilepsy [Pac-Man], Martin Terplan .....(Sep) 250
Patients With Cervical Cancer, Harrison J. Kornfield(Oct) 338
Reply, Joseph Chu, Hisham Tamini .....(Oct) 338
Pot and the Kettle, The, James B. Smith .....(Oct) 339
Pulmonary Embolism in Buerger's Disease, George X. Trimble .....(Jul) 78
Radiology and Medical Care Costs, Richard M. Head .....(Oct) 338
Rising Health Care Costs, Arthur H. Coleman ....(Jul) 76
Serendipitous Diagnosis of Multiple Myeloma by Hemoglobin Electrophoresis, Dennis A. Casciato ....(Nov) 439
Sherlock in the Emergency Room, J. S. Grisolia, W. C. Wiederholt .....(Nov) 438
Sickling Crises at High Altitudes, Preetham Kondlapoodi .....(Aug) 138
Thrombotic Thrombocytopenic Purpura, Gerard P. Sheldon .....(Aug) 140
Traveler's Diarrhea, Irving Shulman .....(Jul) 79
Usefulness of IDA Scanning, Jeffrey L. Kaufman ..(Nov) 437
Waterborne Transmission of *Campylobacter*, Kathy Perkins-Jones, Bob Holman, Floyd Frost .(Oct) 339
Western Student Medical Research Forum, Michael A. Patmas .....(Jul) 80

Corynebacterial Infections, see *Lowly Diphtheroid*
Cost Control in Patient Care, see *Some Economic*
Costs, see *Radiology and Medical Care*
Costs, Health Care, see *Rising*
Costs and Risks of Medical Care—An Annotated Bibliography for Clinicians and Educators (Special Article), Stephen J. McPhee, Lois P. Myers, Steven A. Schroeder .....(Aug) 145
Editorial, Paul J. Sanazaro .....(Aug) 127
Correspondence, Richard M. Head .....(Oct) 338
CT Evidence of Subarachnoid Hemorrhage Due to Presumed Gnathostomiasis, Michael Brant-Zawadzki, Constance B. Wofsy, Gisela Schechter .....(Jul) 65

D

Deafness, see *Cochlear Implants*
Densitometry, see *Bone*
Dermatitis, see *Aminophylline-induced Exfoliative*
Dermatology, see *Perspectives in Occupational*
Dexamethasone Palliation for Metastasis, see *Peptic Ulcer*
Diabetic Retinopathy (Information), Leroy W. Vaughn .....(Sep) 269
Diagnosis of Testicular Torsion (Correspondence), Bruce Haynes .....(Aug) 139
[Diagnostic Clues], see *Bedside Sherlock Holmes*
Diagnostic Workup of Febrile Children Under 24 Months of Age: A Clinical Review, Michael Soman ....(Jul) 1
Editorial, Moses Grossman .....(Jul) 60
Diarrhea, see *Traveler's*
Diarrhea, Chronic, see *Campylobacter* Colitis
[Diet], see *Fasting*
Differential Diagnosis of Pleural Effusions (Medical Progress), Steven A. Sahn .....(Aug) 99
Editorial, Gennaro M. Tisi .....(Aug) 124
Correspondence:
Preetham Kondlapoodi .....(Nov) 435
James B. D. Mark .....(Nov) 435
Diffuse Malignant Mesothelioma: A Review (Occupational Disease—New Vistas for Medicine), William N. Rom, James E. Lockey .....(Dec) 548
Diphtheroid, see *Lowly*
Disease, Index of, see *Foul Tongue*

Distinction in Terminology (Correspondence), Joel A. Stettner ....(Nov) 442
Diuretic Use, see *Clinical Features of Covert*
Don't Kid Around (Editorial), Thomas K. Hunt ..(Aug) 128
[Drug Abuse], see *'Loads' Alert*

E

Ear Effusion in Children, see *Middle*
[Eclampsia], see *Isolated . . . Blindness in Pregnancy*

Editorials: (General and Scientific)
Acquired Immune Dysfunction in Homosexual Men, Arthur J. Ammann ....(Nov) 419
AMA and a National Health Policy ....(Aug) 126
Correspondence, Joseph F. Boyle ....(Nov) 436
Calcium Channel Blockers and Cardiovascular Therapeutics, Bramah N. Singh ....(Jul) 62
Don't Kid Around, Thomas K. Hunt ....(Aug) 128
Enigma of the Eosinophil, Paul B. Beeson ....(Sep) 239
Fasting, Thomas J. Merimee ....(Nov) 418
Febrile Infants: A Commentary, Moses Grossman ..(Jul) 60
Flawed Theories in a Real World ....(Jul) 62
Further Comments on Pleural Effusions, Gennaro M. Tisi ....(Aug) 124
How About Organizing 'Friends of Medicine'? ....(Nov) 421
In Defense of the Bladder, Calvin M. Kunin ....(Sep) 237
Is It Time for a Fundamental Reexamination of Medical Education? ....(Nov) 417
Mast Cells and Homeostasis: Another View, Robert A. Lewis ....(Sep) 234
NMR: Diagnostic Wave of the Future, Gerald M. Pohost ....(Oct) 319
On Having Encounters With Patients ....(Aug) 129
Correspondence, James B. Smith ....(Oct) 339
Overdose With Tricyclic Antidepressants, Rene A. Langou ....(Nov) 422
Paranoia and Nuclear Armaments ....(Sep) 236
Payors' Revolt ....(Sep) 234
Poison Control Centers—Vital Community Resource, Charles E. Becker, Theodore G. Tong ....(Oct) 320
Some Economic and Human Aspects of Cost Control in Patient Care, Paul J. Sanazaro ....(Aug) 127
Therapeutic Issues in Turner's Syndrome, Felix A. Conte, Melvin M. Grumbach ....(Jul) 61
Thoughts on the Past, Present and Future of *WJM* (Oct) 317
Tobacco and Cancer, John H. Holbrook ....(Aug) 125
WJM Welcomes WMS ....(Aug) 124

Effects on the Liver of Chemicals Encountered in the Workplace (Occupational Disease—New Vistas for Medicine), Susan M. Pond ....(Dec) 506
Electrophoresis, Hemoglobin, see *Serendipitous Diagnosis*
Embolism, see *Pulmonary*
[Emergency Physicians], see *Distinction in Terminology*
Emergency Room, see *Sherlock in*
Encounters, Patients, see *On Having*
Endocarditis, see *Infective*
Enigma of the Eosinophil (Editorial), Paul B. Beeson ....(Sep) 239
Enteritis, see Campylobacter
[Environment], see *Occupationl Disease—New Vistas for Medicine*
Eosinophilia, see *Rash and*
Epidemiology (Cancer), see *Occupational*
Epithelial Ovarian Malignancy, see *Recent Progress*

Epitomes:
General and Family Practice ....(Jul) 53
Allergy ....(Aug) 116
Otolaryngology/Head and Neck Surgery ....(Sep) 228
Neurology ....(Oct) 310
Orthopedics ....(Nov) 408

Ethical Problems in Medical Practice—A Protocol for the Guidance of Physicians (Medical Ethics), Malcolm S. M. Watts, Corrine Bayley, Francis A. Healy, Willard S. Osibin, Mindy Werner, Laurens P. White ....(Jul) 83
Correspondence:
Marvin J. Shapiro ....(Sep) 251
John M. Goldenring ....(Sep) 251
Hugh A. Frank ....(Sep) 252
Ethical Protocol, see *Comments on*
Evaluation of Anemia (Topics in Primary Care Medicine), Stephen J. McPhee ....(Sep) 253
Evolution of Occupational Health and the Role of Government, The (Occupational Disease—New Vistas for Medicine), Richard Wade ....(Dec) 577
[Evolving Trends in Society, CMA Committee Report], see *Medical Ethics*

F

Family Practice, General and, see *Epitomes*
Fasting: The History, Pathophysiology and Complications (Medical Progress), Peter R. Kerndt, James L. Naughton, Charles E. Driscoll, David A. Loxterkamp .(Nov) 379
Editorial, Thomas J. Merimee ....(Nov) 418
Fragile-X-Linked Mental Retardation and Macro-Orchidism, Byron C. Moore, Thomas W. Glover, Barbara Kaiser-McCaw, Frederick Hecht ....(Oct) 278
Febrile Children Under 24 Months of Age, see *Diagnostic Workup of*
Febrile Infants: A Commentary (Editorial), Moses Grossman ....(Jul) 60
Flawed Theories in a Real World (Editorial) ....((Jul) 62
Folliculitis, see *Hot Tub*
Food Testing, see *Challenge*
Foot, see *Needle in*
Foul Tongue: A 19th Century Index of Disease (History of Medicine), John S. Haller, Jr. ....(Sep) 258
'Friends of Medicine,' see *How About Organizing*
Further Comments on Pleural Effusions (Editorial), Gennaro M. Tisi ....(Aug) 124

G

General and Family Practice, see *Epitomes*
[Genetic Disease], see *Turner's Syndrome*
Gnathostomiasis, see *CT Evidence of*
Government, Occupational Health and, see *Evolution*
Granulomatosis, Wegener's, see *Survival After Intracerebral Hemorrhage*

H

Hazard Evaluation System and Information Service: A Physician's Resource in Toxicology and Occupational Medicine (Occupational Disease—New Vistas for Medicine), Kim Hooper ....(Dec) 560
Head and Neck Surgery, Otolaryngology, see *Epitomes*
Health Care Costs, see *Rising*

Health Care Delivery:
Model Poison Control System, A, Theodore G. Tong, Charles E. Becker, Donna Foliart, Linda Morse .(Oct) 346
Editorial, Charles E. Becker, Theodore G. Tong .(Oct) 320
Medical Evaluation of Preoperative Patients, Diane L. Elliot, Douglas H. Linz, Joseph A. Kane ....(Oct) 351
Physician Behavior Modification Using Claims Data: Tetracycline for Upper Respiratory Infection, Thomas S. McConnell, Alice H. Cushing, Arthur D. Bankhurst, James L. Healy, Patricia A. McIlvenna, Betty J. Skipper ....(Nov) 448

Health Care System, see *'Opening Up'*
Health Effects of Shift Work (Occupational Disease—New Vistas for Medicine), Joseph LaDou ....(Dec) 525
Health Policy, National, see *AMA*

Hearing Conservation in Industry (Occupational Disease —New Vistas for Medicine), Robert A. Dobie ..(Dec) 499
Heart Transplants (Medical Practice Questions) ..(Oct) 360
Hematologic Improvement Following Splenectomy for Hemoglobin-H Disease, Gail M. Wagner, Stephen A. Liebhaber, Hunter O. Cutting, Stephen H. Embury .....(Oct) 325
Hemoglobin E in Indochinese Refugees, Thomas M. Cunningham .....(Sep) 186
Hemoglobin Electrophoresis, see *Serendipitous Diagnosis*
Hemoglobin-H Disease, see *Hematologic Improvement*
Heparin-Induced Thrombocytopenia (Correspondence):
Robert A. Baird .....(Jul) 80
Sebastian Conti .....(Jul) 81
Reply, Kenneth M. Moser .....(Jul) 81
High Altitudes, see *Sickling Crises*
High Rock, High Tech and Karl Marx (Correspondence), E. R. W. Fox .....(Nov) 441

History of Medicine:
Foul Tongue: 19th Century Index of Disease, John S. Haller, Jr. .....(Sep) 258

Holistic Medicine: Advances and Shortcomings (Correspondence), Edward Shapiro .....(Aug) 139
Homeostasis, see *Mast Cells*
Homosexual Men, see *Acquired Immune Dysfunction*
Homosexual Men, see Pneumocystis *Lung Disease*
[Hospices], see *Care for Terminally Ill*
Hot Tub Folliculitis—A Clinical Syndrome, Barry J. Zacherle, Diane S. Silver .....(Sep) 191
How About Organizing 'Friends of Medicine'? (Editorial) .....(Nov) 421
How Much Testing Is Needed? (Correspondence), Ralph C. Jung .....(Aug) 138
Human Tumor Stem Cell Assay (Medical Practice Questions) .....(Dec) 559
Hypercalcemia, see *Hypervitaminosis A: A Cause of*
Hypervitaminosis A: A Cause of Hypercalcemia, Sunita C. Baxi, George E. Dailey III .....(Nov) 429

I

IDA Scanning, see *Usefulness*
Imaging, see *Nuclear Magnetic Resonance*
Imaging Tests, see *Acute Cholecystitis: Diagnostic Role*
Immune System, see *Methylethylketone Damage*
Immunobiologics, see *Sources of Supply of Selected*
Immunoglobulin A and the Kidney (Medical Staff Conference) .....(Oct) 302
Impaired Physician, see *California Model for Treatment*
Implants, see *Cochlear*
In Defense of the Bladder (Editorial), Calvin M. Kunin .....(Sep) 237
Indochinese Refugees, see *Hemoglobin E in*
Industrial Hygiene Data: Compliance, Dosage and Clinical Relevance (Occupational Disease—New Vistas for Medicine), Stephen M. Rappaport, Robert C. Spear, Janice W. Yager .....(Dec) 572
Industry, see *Hearing Conservation*
Infant Passenger Safety Education in Perinatal Services in California (Preventive Medicine), Albert Chang, Esther Levy .....(Aug) 162
Editorial, Thomas K. Hunt .....(Aug) 128
Correspondence:
Christine Cassel .....(Nov) 437
Rick Leskowitz .....(Nov) 438
Infants, see *Febrile*
Infectious Mononucleosis, see *Clinical Aspects of*
Infective Endocarditis Due to Anaerobic and Microaerophilic Bacteria, Francisco L. Sapico, Radha J. Sarma .....(Jul) 18

Information:
Bedside Sherlock Holmes, The Faith T. Fitzgerald, Lawrence H. Tierney, Jr ...(Aug) 169
Correspondence, J. S. Grisolia, W. C. Wierderholt(Nov) 438
Correspondence, Joel A. Stettner .....(Nov) 442
California Model for Treatment of the Impaired Physician, Robert Larsen .....(Sep) 265
Diabetic Retinopathy, Leroy W. Vaughn .....(Sep) 269
'Loads' Alert, Ali M. Khajawall, John J. Sramek, Jr., George M. Simpson .....(Aug) 166
Scope of Practice, C. John Tupper .....(Nov) 467
Sources of Supply of Selected Immunobiologics: 1982, S. Benson Werner .....(Nov) 468

Insulinoma, see *Value of Artificial Beta Cell*
Intermittent Positive Pressure Breathing [IPPB] (Medical Practice Questions) .....(Dec) 576
Ionizing Radiation and Its Risks (Occupational Disease—New Vistas for Medicine), Marvin Goldman ...(Dec) 540
[IPPB], see *Intermittent*
Is It Time for a Fundamental Reexamination of Medical Education? (Editorial) .....(Nov) 417
Isolated Cortical Blindness in Pregnancy, Robert N. Nishimura, Richard Koller .....(Oct) 335
Isopropanol Poisoning, see *Peritoneal Dialysis*

K

Key Elements of the Occupational History for the General Physician (Occupational Disease—New Vistas for Medicine), Charles E. Becker .....(Dec) 581
Kicking the Habit: Benefits and Methods of Quitting Cigarette Smoking (Topics in Primary Care Medicine), Steven R. Cummings .....(Nov) 443
Kidney, see *Immunoglobulin A and*

L

Lead, see *Occupational and Community Exposures*
[Leukemia, Acute Lymphoblastic], see *Rash and Eosinophilia*
Leukemia in Hospital Patients With Occupational Exposure to the Sawmill Industry (Correspondence), John A. Burkart .....(Nov) 440
Liver, see *Effects on . . . of Chemicals*
Liver Biopsy, see *Bleeding After*
'Loads' Alert (Information), Ali M. Khajawall, John J. Sramek, Jr, George M. Simpson .....(Aug) 166
Lowly Diphtheroid: Nondiphtheria Corynebacterial Infections in Humans (Medical Staff Conference) ....(Jul) 45
Lung Disease, see *Pneumocystis*
[Lungs, Effect of Volcanic Ash], see *Specialty Conferences*

M

Macro-Orchidism, see *Fragile-X-Linked Mental Retardation*
Male Occupational Reproductive Hazards (Occupational Disease—New Vistas for Medicine), M. Donald Whorton .....(Dec) 521
Mast Cell in Allergic Diseases and Mastocytosis (Medical Progress), Diana L. Marquardt, Stephen I. Wasserman .....(Sep) 195
Editorial, Robert A. Lewis .....(Sep) 234
Mast Cells and Homeostasis: Another View (Editorial) .....(Sep) 234
Mastocytosis, see *Mast Cell*
Medical Adventure in South America (Medicine in Perspective), William L. Minkowski .....(Nov) 451
Medical Care . . . Bibliography, see *Costs and Risks of*
Medical Education, see *Is It Time*

Medical Ethics:
Ethical Problems in Medical Practice—A Protocol for the Guidance of Physicians, Malcolm S. M. Watts, Corrine Bayley, Francis A. Healy, Willard S. Osibin, Mindy Werner, Laurens P. White .....(Jul) 83

Correspondence:
Marvin J. Shapiro ..... (Sep) 251
John M. Goldenring ..... (Sep) 251
Hugh A. Frank ..... (Sep) 252

Medical Evaluation of Preoperative Patients (Health Care Delivery), Diane L. Elliot, Douglas H. Linz, Joseph A. Kane ..... (Oct) 351
Medical Practice, see *Ethical Problems*

Medical Practice Questions:

Bone Densitometry ..... (Nov) 459
Challenge Food Testing for Respiratory Disorders . (Sep) 194
Challenge Food Testing for Rheumatoid Arthritis .. (Oct) 277
Cochlear Implants for Deafness ..... (Nov) 374
Heart Transplants ..... (Oct) 360
Human Tumor Stem Cell Assay ..... (Dec) 559
Intermittent Positive Pressure Breathing [IPPB] ... (Dec) 576
Methylethylketone Damage of the Immune System . (Nov) 447
Photon Absorptionmetric Procedure ..... (Oct) 337
Plasmapheresis ..... (Sep) 257
Reconsideration of Biofeedback ..... (Dec) 530
Reconsideration of Repository Emulsion Therapy . (Nov) 450
Viral/Bacterial Vaccines in the Treatment of Arthritis ..... (Dec) 554

Medical Progress:

Calcium Channel Blockers, Prakash C. Deedwania . (Jul) 24
Editorial, Bramah N. Singh ..... (Jul) 62
Differential Diagnosis of Pleural Effusions, Steven A. Sahn ..... (Aug) 99
Editorial, Gennaro M. Tisi ..... (Aug) 124
Correspondence, Preetham Kondlapoodi, Juan B. Gabriel ..... (Nov) 435
Correspondence, James B. D. Mark ..... (Nov) 435
Mast Cell in Allergic Diseases and Mastocytosis, Diana L. Marquardt, Stephen I. Wasserman ..... (Sep) 195
Editorial, Robert A. Lewis ..... (Sep) 234
Nuclear Magnetic Resonance Imaging: Current Capabilities, Peter L. Davis, Lawrence E. Crooks, Alexander R. Margulis, Leon Kaufman ..... (Oct) 290
Editorial, Gerald M. Pohost ..... (Oct) 319
Fasting: The History, Pathophysiology and Complications, Peter R. Kerndt, James L. Naughton, Charles E. Driscoll, David A. Loxterkamp ..... (Nov) 379
Editorial, Thomas J. Merimee ..... (Nov) 418

Medical School, see *Cheating Beyond*

Medical Staff Conferences:

The Lowly Diphtheroid: Nondiphtheria Corynebacterial Infections in Humans, Chief Discussant: Richard M. Locksley ..... (Jul) 45
Rheumatoid Arthritis—From Rubens to Restriction Maps, Chief Discussant: John D. Stopo ..... (Aug) 109
Immunoglobulin A, Chief Discussant: James L. Naughton ..... (Oct) 302
Pneumocystis Lung Disease in Homosexual Men, Chief Discussant: Jeffrey Golden ..... (Nov) 400
Editorial, Arthur J. Ammann ..... (Nov) 419

Medicine, Clinical, Advances, see *Epitomes*
Medicine,' 'Friends of, see *How About*

Medicine in Perspective:

Medical Adventure in South America, William L. Minkowski ..... (Nov) 451

Men, Counseling, see *Urology/Sexuality Clinic*
Mental Retardation, see *Fragile-X-Linked*
Mercury, see *Occupational and Community Exposures*
Mesothelioma, see *Diffuse Malignant*
Metaldehyde Poisoning From Slug Bait Ingestion, W. T. Longstreth, Jr., David J. Pierson ..... (Aug) 134
Methylethylketone Damage of the Immune System (Medical Practice Questions) ..... (Nov) 447
Middle Ear Effusion in Children: A Report of Treatment in 500 Cases, Brian D. Forquer, Fred H. Linthicum, Jr. ..... (Nov) 370
Milk, Raw, see Campylobacter *Enteritis*
Model Poison Control System, A (Health Care Delivery), Theodore G. Tong, Charles E. Becker, Donna Foliart, Linda Morse ..... (Oct) 346
Editorial, Charles E. Becker, Theodore G. Tong . (Oct) 320
[Mount St Helens], see *Ash Babies*
Mount St Helens, see *Specialty Conferences*
Mushroom Poisoning, see Amanita phalloides-*Type*
Myeloma, see *Serendipitous Diagnosis*
Myoglobinuria With Adenovirus Infection, see *Association of*
[Myringotomy], see *Middle Ear Effusion*

N

National Health Policy, see *AMA*
Neck, Head and, Surgery, Otolaryngology, see *Epitomes*
Needle in the Foot (Correspondence), Lawrence H. Wanetick, Richard Hill ..... (Aug) 140
Neurology, see *Epitomes*
Neuropathies, Peripheral, see *Occupational*
New Training Opportunities in Occupational Health (Page End), James P. Hughes ..... (Dec) 524
NMR: Diagnostic Wave of the Future (Editorial), Gerald M. Pohost ..... (Oct) 319
Nuclear Armaments, see *Paranoia*
Nuclear Armaments (Correspondence):
Christine K. Cassel ..... (Nov) 437
Rick Leskowitz ..... (Nov) 438
Nuclear Magnetic Resonance Imaging: Current Capabilities (Medical Progress), Peter L. Davis, Lawrence E. Crooks, Alexander R. Margulis, Leon Kaufman . (Oct) 290
Editorial, Gerald M. Pohost ..... (Oct) 319
Nutrition, Parenteral, see *Anergy in High-Risk . . . Patients*

O

Occupational and Community Exposures to Toxic Metals: Lead, Cadmium, Mercury and Arsenic, (Occupational Disease—New Vistas for Medicine), Philip J. Landrigan ..... (Dec) 531
Occupational Asthma (Occupational Disease—New Vistas for Medicine), Dean Sheppard ..... (Dec) 480

Occupational Disease—New Vistas for Medicine:

Introduction: The Tip of a Huge Iceberg?, Malcolm S. M. Watts ..... (Dec) 477
Occupational Medicine—Long History and Bright Future, Charles E. Becker ..... (Dec) 478
Occupational Asthma, Dean Sheppard ..... (Dec) 480
Perspectives in Occupational Dermatology, C. G. Toby Mathias, Howard I. Maibach ..... (Dec) 486
Occupational Peripheral Neuropathies, Marcello Lotti, Charles E. Becker, Michael J. Aminoff ..... (Dec) 493
Hearing Conservation in Industry, Robert A. Dobie (Dec) 499
Effects on the Liver of Chemicals Encountered in the Workplace, Susan M. Pond ..... (Dec) 506
Occupational Work Evaluation of Patients With Cardiac Disease: A Guide for Physicians, Robert Frank DeBusk, Charles Andrew Dennis ..... (Dec) 515
Male Occupational Reproductive Hazards, M. Donald Whorton ..... (Dec) 521
Health Effects of Shift Work, Joseph LaDou ..... (Dec) 525
Occupational and Community Exposures to Toxic Metals: Lead, Cadmium, Mercury and Arsenic, Philip J. Landrigan ..... (Dec) 531
Ionizing Radiation and Its Risks, Marvin Goldman (Dec) 540
Diffuse Malignant Mesothelioma: A Review, William N. Rom, James E. Lockey ..... (Dec) 548

Occupational Epidemiology: Detection of Cancer in the Workplace, John M. Peters, William E. Wright, David H. Garabrant .....(Dec) 555
Hazard Evaluation System and Information Service: A Physician's Resource in Toxicology and Occupational Medicine, Kim Hooper .....(Dec) 560
Industrial Hygiene Data: Compliance, Dosage and Clinical Relevance, Stephen M. Rappaport, Robert C. Spear, Janice W. Yager .....(Dec) 572
Evolution of Occupational Health and the Role of Government, The, Richard Wade .....(Dec) 577
Key Elements of the Occupational History for the General Physician, Charles E. Becker .....(Dec) 581
Page End: New Training Opportunities in Occupational Health, James P. Hughes .....(Dec) 524

Occupational Epidemiology: Detection of Cancer in the Workplace (Occupational Disease—New Vistas for Medicine), John M. Peters, William E. Wright, David H. Garabrant .....(Dec) 555
Occupational Exposure to Sawmill Industry, see *Leukemia*
Occupational History, see *Key Elements of*
Occupational Medicine—Long History and Bright Future (Occupational Disease—New Vistas for Medicine), Charles E. Becker .....(Dec) 478
Occupational Peripheral Neuropathies (Occupational Medicine—New Vistas for Medicine), Marcello Lotti, Charles E. Becker, Michael J. Aminoff .....(Dec) 493
Occupational Work Evaluation of Patients With Cardiac Disease (Occupational Disease—New Vistas for Medicine), Robert Frank DeBusk, Charles Andrew Dennis .....(Dec) 515
On Having Encounters With Patients (Editorial) .(Aug) 129
Correspondence, James B. Smith .....(Oct) 339
'Opening Up' the Health Care System (Correspondence), Gregory E. Polito .....(Jul) 82
Orthopedics, see *Epitomes*
Ovarian Malignancy, see *Recent Progress in Treatment*
Overdose With Tricyclic Antidepressants (Editorial), Rene A. Langou .....(Nov) 422

P

Pacilepsy [Pac-Man] (Correspondence), Martin Terplan .....(Sep) 250
Pac-Man, see *Pacilepsy*
Pain, see *Shoulder*
Paranoia and Nuclear Armaments (Editorial) .....(Sep) 236
Parents, Adoptive and Birth, see *Birth*
Patients, Encounters, see *On Having*
Patients With Cervical Cancer (Correspondence), Harrison J. Kornfield .....(Oct) 338
Reply, Joseph Chu, Hisham Tamini .....(Oct) 338
Payors' Revolt, The (Editorial) .....(Sep) 234
Peptic Ulcer Disease and Other Complications in Patients Receiving Dexamethasone Palliation for Brain Metastasis, Richard D. Pezner, James A. Lipsett .(Nov) 375
Perinatal Services, see *Infant Passenger Safety*
Peritoneal Dialysis for Isopropanol Poisoning, Mark B. Mecikalski, Thomas A. Depner .....(Oct) 322
Peripheral Neuropathies, see *Occupational*
Perspectives in Occupational Dermatology (Occupational Disease—New Vistas for Medicine), C. G. Toby Mathias, Howard I. Maibach .....(Dec) 486
Photon Absorptionmetric Procedure (Medical Practice Questions) .....(Oct) 337
Physician, Impaired, see *California Model for Treatment*
Physician Behavior Modification Using Claims Data: Tetracycline for Upper Respiratory Infection, Thomas S. McConnell, Alice H. Cushing, Arthur D. Bankhurst, James L. Healy, Patricia A. McIlvenna, Betty J. Skipper .....(Nov) 448
[Pig Fertilizer], see Ascaris *Infection*
Plasmapheresis (Medical Practice Questions) .....(Sep) 257
Pleural Effusions, see *Differential Diagnosis*
Pleural Effusions, see *Further Comments*
Pneumocystis Lung Disease in Homosexual Men, see *Medical Staff Conferences*
Poison Control Centers—Vital Community Resource (Editorial), Charles E. Becker, Theodore G. Tong ...(Oct) 320
Poison Control System, see *Model*
Poisoning, see *Peritoneal Dialysis*
Poisoning, Mushroom, see Amanita phalloides
Poisoning [Slug Bait], see *Metaldehyde*
Polyarthritis Associated With Breast Carcinoma, Michael Kwok L. Chan, Charles S. Hendrickson, Kathleen E. Taylor .....(Aug) 132
Pot and the Kettle, The (Correspondence), James B. Smith .....(Oct) 339
Practice [Monitoring Medical], see *Scope of*
Pregnancy, see *Isolated Cortical Blindness*
Preoperative Patients, see *Medical Evaluation*

Preventive Medicine:

Infant Passenger Safety Education in Perinatal Services in California, Albert Chang, Esther Levy .....(Aug) 162
Editorial, Thomas K. Hunt .....(Aug) 128
Correspondence:
Christine Cassel .....(Nov) 437
Rick Leskowitz .....(Nov) 438

Primary Care Medicine, see *Topics in*
[*Pseudomonas aeruginosa* Rash], see *Hot Tub Folliculitis*
Pulmonary Embolism in Buerger's Disease (Correspondence), George X. Trimble .....(Jul) 78

Q

Quality of Care of Women With Stage I Cervical Cancer, Joseph Chu, Lincoln Polissar, Hisham K. Tamimi (Jul) 13
Correspondence, Harrison J. Kornfield .....(Oct) 338
Reply, Joseph Chu, Hisham Tamini .....(Oct) 338

R

Radiology and Medical Care Costs (Correspondence), Richard M. Head .....(Oct) 338
Radiation, see *Ionizing*
[Rash], see *Hot Tub Folliculitis*
Rash and Eosinophilia in a 23-Year-Old Man (Clinicopathologic Conference), see *Specialty Conferences*
Recent Developments in the Diagnosis and Treatment of Urinary Tract Infections, see *Specialty Conferences*
Recent Progress in the Treatment of Epithelial Ovarian Malignancy, Jonathan S. Berek, Neville F. Hacker, Leo D. Lagasse .....(Oct) 273
Reconsideration of Biofeedback (Medical Practice Questions) .....(Dec) 530
Reconsideration of Repository Emulsion Therapy (Medical Practice Questions) .....(Nov) 450
Refugees, see *Hemoglobin E in Indochinese*
Repository Emulsion Therapy, see *Reconsideration*
Reproductive Hazards, see *Male*
Respiratory Disorders, see *Challenge*
Retardation, see *Fragile-X-Linked Mental*
Retinopathy, see *Diabetic*
Rheumatoid Arthritis, see *Challenge Food Testing*
Rheumatoid Arthritis—From Rubens to Restriction Maps, (Medical Staff Conference) .....(Aug) 109
Rising Health Care Costs (Correspondence), Arthur H. Coleman .....(Jul) 76
Risks of Medical Care, see *Costs and*

S

Safety Education in Perinatal Services, see *Infant Care*

[San Fran cco], see *Model Poison Control System*
Sawmill industry, see *Leukemia*
Scope of Practice (Information), C. John Tupper ..(Nov) 467
Serendipitous Diagnosis of Multiple Myeloma by Hemoglobin Electrophoresis (Correspondence), Dennis A. Casciato .....(Nov) 439
Sexuality Clinic, see *Urology*
[Sexually Transmitted Diseases], see *Recent Developments in Diagnosis . . . Urinary Tract Infections*
Sherlock Holmes, see *Bedside*
Sherlock in the Emergency Room (Correspondence), J. S. Grisolia, W. C. Wiederholt .....(Nov) 438
Shift Work, see *Health Effects*
Shoulder Pain (Topics in Primary Care Medicine), Richard H. White .....(Oct) 340
Sickling Crises at High Altitudes (Correspondence), Preetham Kondlapoodi .....(Aug) 138
Slug Bait Poisoning, see *Metaldehyde*
Some Economic and Human Aspects of Cost Control in Patient Care (Editorial), Paul J. Sanazaro .....(Aug) 127
Sources of Supply of Selected Immunobiologics: 1982 (Information), S. Benson Werner .....(Nov) 468
South America, see *Medical Adventure*

Special Articles:

Costs and Risks of Medical Care—An Annotated Bibliography for Clinicians and Educators, Stephen J. McPhee, Lois P. Myers, Steven A. Schroeder .....(Aug) 145
Editorial, Paul J. Sanazaro .....(Aug) 127
Correspondence, Richard M. Head .....(Oct) 338
Anatomy, Physiology and Pathology of Biomedical Information, Harold M. Schoolman .....(Nov) 460

Specialty Conferences:

Turner's Syndrome (Clinical Genetics Conference, Children's Orthopedic Hospital and Medical Center, Seattle, and University of Washington), Participants: Judith G. Hall, Virginia P. Sybert, Roger A. Williamson, Nancy L. Fisher, Susan D. Reed .....(Jul) 32
Editorial, Felix A. Conte .....(Jul) 61
Recent Developments in the Diagnosis and Treatment of Urinary Tract Infections (University of Washington), Discussant: Walter E. Stamm .....(Sep) 213
Editorial, Calvin M. Kunin .....(Sep) 237
Rash and Eosinophilia in a 23-Year-Old Man (Clinicopathologic Conference, The Oregon Health Sciences University), Discussants: Ray Bachhuber, John H. Fitchen, Barbara Harty-Golder .....(Sep) 221
Editorial, Paul B. Beeson .....(Sep) 239
Are Volcanoes Hazardous to Your Health? What Have We Learned From Mount St Helens? (Oregon Health Sciences University, Biological Effects of Volcanic Ash (BEVA) Study Center, Department of Medicine, Medical Grand Rounds), Discussant: A. Sonia Buist .(Oct) 294

Splenectomy for Hemoglobin-H Disease, see *Hematologic*
Subarachnoid Hemorrhage Due to Presumed Gnathostomiasis, see *CT Evidence of*
Surgical Patients, see *Anergy in High-Risk*
Survival After Intracerebral Hemorrhage in Wegener's Hemorrhage, Christopher Baillie Hearne, Edward T. Zawada, Jr. .....(Nov) 431
Syndrome, see *Turner's*

T

Terminally Ill, see *Care for*
Testicular Torsion, see *Diagnosis of*
Tests, Imaging, see *Acute Cholecystitis*
Tetracycline for . . . Infection, see *Physician Behavior Modification*
Therapeutic Issues in Turner's Syndrome (Editorial), Felix A. Conte, Melvin M. Grumbach .....(Jul) 61
Thoughts on the Past, Present and Future of WJM (Editorial) .....(Oct) 317
Thrombocytopenia see *Heparin-Induced*
Thrombotic Thrombocytopenic Purpura (Correspondence), Gerard P. Sheldon .....(Aug) 140
Tip of a Huge Iceberg?, The (Introduction to Occupational Disease—New Vistas for Medicine), Malcolm S. M. Watts .....(Dec) 477
Tobacco and Cancer (Editorial), John H. Holbrook (Aug) 125
Tongue, see *Foul*

Topics in Primary Care Medicine:

Clinical Aspects of Infectious Mononucleosis, Maxine A. Papadakis .....(Aug) 141
Evaluation of Anemia, Stephen J. McPhee .....(Sep) 253
Shoulder Pain, Richard H. White .....(Oct) 340
Kicking the Habit: Benefits and Methods of Quitting Cigarette Smoking, Steven R. Cummings .....(Nov) 443

Toxic Metals, see *Occupational and Community Exposures*
Toxicology, see *Hazard Evaluation*
Training, Occupational Health, see *New*
Transient Bifascicular Block Following Blunt Chest Trauma, Kenneth W. Carr, Allen D. Johnson, Gabriel Gregoratos .....(Sep) 245
Transplants, see *Heart*
Trauma, see *Transient Bifascicular Block*
Traveler's Diarrhea (Correspondence), Irving Shulman .....(Jul) 79
Tricyclic Antidepressant Ingestion, see *Admission Criteria*
Tricyclic Antidepressants, see *Overdose With*
Tuberculous Peritonitis, see *Bilious Ascites*
Tumor, Stem Cell Assay, see *Human*
Turner's Syndrome, see *Specialty Conferences*

U

Ulcer, see *Peptic*
Urinary Tract Infections, see *Recent Developments*
Urology/Sexuality Clinic: Results of Counseling of 67 Men, Alex L. Finkle, Shirley Jackson .....(Aug) 95
Usefulness of IDA Scanning, (Correspondence), Jeffrey L. Kaufman .....(Nov) 437

V

Vaccines, see *Viral/Bacterial*
Value of Artificial Beta Cell in the Management of Insulinoma, Lubomir J. Valenta, Harvey Eisenberg, Don R. Miller, Sterling M. Tanner, Stephen G. Romansky, Arthur H. Rubenstein, Mary Mako, Bruce F. Cullen, Michael P. Golden, Alan N. Elias .....(Jul) 67
Viral/Bacterial Vaccines in the Treatment of Arthritis (Medical Practice Questions) .....(Dec) 554
Vitamin A, see *Hypervitaminosis*
Volcanoes Hazardous to Health?, see *Specialty Conferences*

W

Washington State, see Ascaris *Infection*
Waterborne Transmission of *Campylobacter* (Correspondence), Kathy Perkins-Jones, Bob Holman, Floyd Frost .....(Oct) 339
Wegener's Granulomatosis, see *Survival*
WESTERN JOURNAL OF MEDICINE, see *Thoughts on Past, Present and Future*
Western Student Medical Research Forum (Correspondence), Michael A. Patmas .....(Jul) 80
WJM, see *Thoughts on Past, Present and Future*
WJM Welcomes WMS (Editorial) .....(Aug) 124
Women With Cervical Cancer, see *Quality of Care of*
Work Evaluation, see *Occupational*
[Workplace], see *Occupational Disease—New Vistas for Medicine*
Wyoming Medical Society, see *WJM Welcomes*

(Continued from Page 35)

April 20-22—**8th Annual Symposium—Care of the Sick Newborn.** Memorial Hospital Medical Center-UCI Center for Health Education. Long Beach. Wednesday-Friday. 17 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

PSYCHIATRY

January 3-7—**Couple and Family Therapy: Conflict and Change.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $150. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 9-13—**Mental Research Institute—Winter Seminar.** Palo Alto. Sunday-Thursday. 27 hrs. $270. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 17-21—**Divorce Mediation.** Mental Research Institute, Palo Alto. Monday-Friday. 15 hrs. $155. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

January 22—**The Many Faces of Domestic Violence.** UCLA. Saturday. 6 hrs. $90.

January 23-28—**9th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 26 hrs. $265.

January 29—**Heinz Von Foerster on Applications of the Constructivist Perspective in Family Therapy.** Mental Research Institute, Palo Alto. Saturday. 6 hrs. $85. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

February 3-6—**Cognitive, Emotional and Neurophysiologic Effects of Head Trauma: Post-Concussion Syndrome.** So. Calif. Neuropsychiatric Institute at La Quinta Hotel, La Quinta. Thursday-Sunday. 15 hrs. Contact: Gail Waldron, MD. SCNPI, 6794 La Jolla Blvd., La Jolla 92037. (619) 454-2102.

February 26-27—**Biobehavioral Science for Psychiatrists.** STAN. Saturday-Sunday. 11 hrs. $250.

February 26-27—**Beyond the Relaxation Response: Self-Regulation Mechanisms and Clinical Strategies.** UCLA. Saturday-Sunday.

RADIOLOGY AND PATHOLOGY

January 10-13—**Imaging Symposium.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, Coronado. Monday-Thursday. 27 hrs. $350. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

January 15-16—**Digital Subtraction Angiography Course.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday. $200.

January 17-21—**Advanced Microbiology: Recent Developments and New Frontiers.** American Society of Clinical Pathologists at Holiday Inn-Fisherman's Wharf, San Francisco. Monday-Friday. 32 hrs. $600/$700. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

January 17-21—**Interventional Radiology and Diagnostic Imaging Modalities.** UCSF at Fairmont, San Francisco. Monday-Friday. 33 hrs. $400.

January 23-28—**11th Annual Diagnostic Radiology Seminars.** UCSF at Waiohai Hotel, Kauai. Sunday-Friday. 30 hrs. $375.

January 24-27—**Chest Radiology 1983.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Thursday. 24 hrs. $300. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

February 2-4—**5th Annual Immunoassay Conference.** Scripps Clinic and Research Foundation at Vacation Village, San Diego. Wednesday-Friday. 21 hrs. $250. Contact: Dianne Tisue, Dept. of Academic Affairs, Scripps Clinic and Research Fndn., 10666 N. Torrey Pines Rd., La Jolla 92037. (619) 455-9100.

February 2-4—**10th Annual Course in Genitourinary Pathology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Wednesday-Friday. 23 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

February 2-7—**Society of Nuclear Medicine—2nd Conjoint Winter Congress.** Cathedral Hill Hotel, San Francisco. Wednesday-Monday. Contact: SNM, Meetings Dept., 475 Park Ave. So., New York 10016. (212) 889-0717.

February 4-6—**35th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza, Los Angeles. Friday-Sunday. $125, members; $175, nonmembers. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 6-11—**5th Annual Winter Conference in the High Sierra—OB/GYN Imaging.** American College of Medical Imaging at Sahara, Lake Tahoe. Sunday-Friday. 25 hrs. $347, members; $385, nonmembers. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

February 6-12—**Los Angeles Radiological Society—Annual Post Convention Seminar.** Hyatt Regency, Kaanapau, Maui. One week. 20 hrs. Contact: Diane Johnson, LARS, P.O. Box 57278, Los Angeles 90057. (213) 484-5120.

February 9-12—**Nuclear Radiology.** UCSD at Hotel del Coronado, Coronado. Wednesday-Saturday. 20 hrs. $335. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

February 14-18—**Current Methods in Blood Banking and Immunohematology.** American Society of Clinical Pathologists at Town and Country, San Diego. Monday-Friday. 31½ hrs. $560/$660. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

February 23-25—**New Imaging Modalities in Radiology.** Memorial Hospital Medical Center at Hilton Riviera, Palm Springs. Wednesday-Friday. 18 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

March 9-11—**Sierra Radiology Conference.** Sacramento Radiology Research and Education Foundation at North Lake Tahoe. Wednesday-Friday. 18 hrs. $280. Contact: Arthur B. Dublin, MD, Prog. Dir., Sacramento Radiology Research and Education Fndn., P.O. Box 161112, Sacramento 95816.

March 14-18—**Diagnostic Radiology.** UCSF. Monday-Friday. 33 hrs. $400.

March 14-18—**4th Midwinter Diagnostic Radiology Conference on Imaging Modalities in the Chest and Abdomen.** Loyola Univ. at Kapalua Bay Hotel, Maui. Monday-Friday. 20 hrs. $325. Contact: L. Gunzburger, PhD, Div. of Cont. Med. Ed., Loyola Univ. Med. Ctr., 2160 S. 1st Ave., Maywood, IL 60153. (312) 531-3236.

March 18-20—**2nd Annual Ultrasound Update (Abdominal and Obstetrical).** Memorial Hospital of Long Beach and Institute for Medical Studies at Los Angeles. Friday-Sunday. 16 hrs. $300. Contact: Kim Stroich, IMS, 14761 Franklin Ave., Suite A, Tustin 92680. (714) 832-2650.

March 21-25—**Obstetric and Gynecologic Pathology.** American Society of Clinical Pathologists at San Diego. Monday-Friday. 28 hrs. $550/$650. Contact: Marian Macdonald, ASCP, 2100 W. Harrison St., Chicago 60612. (312) 738-1336.

March 23-25—**Current Concepts in Surgical Pathology.** STAN. Wednesday-Friday. 21 hrs. $400.

March 25-26—**Cellular and Molecular Endocrinology.** UC-Riverside and UCLA at UC-Riverside. Friday-Saturday. Contact: Dr. Anthony W. Norman, Dept. of Biochemistry, Univ. of Calif., Riverside 92521. (714) 787-4777.

April 13-15—**Radiology of the Emergency Patient.** UCI at Century Plaza, Los Angeles. Wednesday-Friday. 18 hrs. $295. Contact: Phyllis Roy, UCIMC-Radiology, #103, 101 City Dr. So., Orange 92668. (714) 634-6579.

April 15-17—**B-Scan Ultrasonography: Update.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday. $250.

(Continued on Page 38)

(Continued from Page 37)

SURGERY

December 18—**Super Blood.** Heart Institute of the Desert, Eisenhower Medical Center, Rancho Mirage. Saturday. 1½ hrs. Contact: Heart Inst. of the Desert, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

January 12—**Office Urology.** LLU. Wednesday. 4 hrs.

January 14-15—**10th Annual Santa Clara County Surgical Seminar—Critical Care and Current Concepts.** Santa Clara Co. Surgical Seminar Assn., at Le Baron Hotel, San Jose. Friday-Saturday. 15 hrs. $160. Contact: Surgical Seminar, c/o Kenneth Watanabe, MD, 150 N. Jackson Ave., #209, San Jose 95116.

January 17-19—**Society of Thoracic Surgeons.** Hilton, San Francisco. Monday-Wednesday. Contact: STS, 111 E. Wacker Dr., Chicago 60601.

January 21-22—**5th Annual Postgraduate Course on Surgery.** UCD at Holiday Inn, Sacramento. Friday-Saturday. 14 hrs. $135.

January 24-26—**Midwinter Clinical Conference in Ophthalmology and Otolaryngology.** Research Study Club at Hilton, Los Angeles. Monday-Wednesday. 21 hrs. $200. Contact: Research Study Club, P.O. Box 49412, Los Angeles 90049.

January 29—**Current Status of Prosthetic Valves.** Heart Institute of the Desert, Eisenhower Medical Center, Rancho Mirage. Saturday. 1½ hrs. Contact: Heart Inst. of the Desert, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

January 29—**Practical Use of the Visual Physiology Laboratory.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $50. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 3-5—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute, Los Angeles. Thursday-Saturday. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

February 6-10—**Lake Tahoe Vitreo-Retinal Symposium.** Retina Faculty, UCD, at Granlibakken Ski Resort, Tahoe City. Sunday-Thursday. Contact: Donald May, MD, 2315 Stockton Blvd., Sacramento 95817. (916) 453-2941.

February 14-17—**Musculo-Skeletal Disease—New Diagnostic Concepts and Modalities.** UCSD at Hotel del Coronado, Coronado. Monday-Thursday. 21 hrs. $300. Contact: Mary J. Ryals, Prog. Coordinator, P.O. Box 61203, DFW Airport, Texas 75261. (214) 659-9590.

February 17-19—**Pediatric Urology.** American Urological Assn. at Hilton, San Diego. Thursday-Saturday. 16 hrs. Contact: Alice Henderson, Office of Ed., AUA, P.O. Box 25147, Houston TX 77265. (713) 790-6070.

February 19—**The Dimensions of Cardiac Surgery.** Heart Institute of the Desert, Eisenhower Medical Center, Rancho Mirage. Saturday. 1½ hrs. Contact: Heart Inst. of the Desert, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

February 19-26—**Updates in Trauma: An Epic Medical Expedition.** American Inst. of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

February 23-24—**Neurological Problems.** Federation of Western Neurological Societies and UCLA at UCLA. Wednesday-Thursday. Contact: UCLA.

February 25-26—**Ophthalmology Update on Basic Sciences for the Clinician.** Update: Fndn. for Systematic Postgraduate Education in Ophthalmology, UCD, PMC, UCSF, STAN at San Franciscan Hotel, San Francisco. Saturday-Sunday. Contact: Update, 3910 Sand Hill Rd., Woodside 94062. (415) 563-4321, ext. 2763.

March 7-11—**Surgical Forum.** Soc. of Graduate Surgeons of the Los Angeles Co./USC Med. Ctr. at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. $350. Contact: Dir. of Med. Ed., Soc. of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

March 9-10—**American Orthopaedic Foot Society.** Anaheim. Wednesday-Thursday. 12½ hrs. Contact: Kenneth A. Johnson, MD, Dept. of Orthopedics, Mayo Clinic, Rochester, MN 55905. (507) 284-2778.

March 10-15—**American Academy of Orthopaedic Surgeons.** Convention Center, Anaheim. Thursday-Tuesday. Contact: AAOS, 444 N. Michigan Ave., Chicago 60611.

March 12—**Women vs Men—Long-Term Results of Myocardial Revascularization.** Heart Institute of the Desert, Eisenhower Medical Center, Rancho Mirage. Saturday. 1½ hrs. Contact: Heart Inst. of the Desert, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

March 14-18—**Sports Medicine.** Univ. of Hawaii at Princess Kaiulani Hotel. Waikiki, Honolulu. Monday-Friday. 18 hrs. $250. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu 96822. (808) 948-8244.

March 17-19—**Gynecologic Surgery With Emphasis on Gynecologic Urology.** Memorial Hospital Medical Ctr. at Hilton Riviera, Palm Springs. Thursday-Saturday. 15 hrs. Contact: Asst. Dir., Ctr. for Health Ed., 2801 Atlantic Ave., Long Beach 90801.

March 19-20—**Ophthalmology Update on Basic Sciences for the Clinician.** Update: Fndn. for Systematic Postgraduate Education in Ophthalmology, UCD, PMC, UCSF, STAN at San Franciscan Hotel, San Francisco. Saturday-Sunday. Contact: Update, 3910 San Hill Rd., Woodside 94062. (415) 563-4321, ext. 2763.

March 19-23—**20th Annual Seminar on Controversial Areas in Surgery.** UCLA at Palm Springs. Saturday-Wednesday.

March 23-25—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt, Palo Alto. Wednesday-Friday. 16 hrs. $225.

March 23-27—**11th Annual Symposium on Vascular Surgery.** UCLA at Palm Springs. Wednesday-Sunday.

March 26—**Complications of Myocardial Infarction Surgical Management.** Heart Institute of the Desert, Eisenhower Medical Center, Rancho Mirage. Saturday. 1½ hrs. Contact: Heart Inst. of the Desert, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

April 9-16—**Cardiovascular Medicine and Surgery: An Advanced Course.** See Medicine, April 9-16.

April 15-16—**American Association of Clinical Urologists.** Hilton, Las Vegas. Friday-Saturday. Contact: AACU, 2017 Walnut St., Philadelphia 19117.

April 17-21—**American Urological Association.** Convention Center, Las Vegas. Sunday-Thursday. 35 hrs. $350, nonmembers. Contact: Richard J. Hannigan, Exec. Sec., AUA, 1120 N. Charles St., Baltimore, MD 21201. (301) 727-1100.

April 21-24—**Wound Management Workshop.** Plastic Surgery Research Foundation at Hilton, San Diego. Thursday-Sunday. 20 hrs. Contact: Edith S. Bookstein, 7810 Lookout Dr., La Jolla 92037. (714) 454-3212.

April 22-23—**14th Annual Postgraduate Seminar—Eyelids, Orbit and Lacrimal Apparatus.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. Contact: Lu Hendricks, JSEI, UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

April 30-May 7—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela. One week. 25 hrs. $365.

OF INTEREST TO ALL PHYSICIANS

December 30-31—**Second Annual Potpourri of Medicine Seminar.** Huntington Memorial Hospital, Pasadena. Thursday-Friday. Contact: Arlene M. Ellis, Med. Staff Affairs, Huntington Mem. Hosp., 100 Congress St., Pasadena 91105. (213) 440-5165.

January 15-23—**Intensive Course in Geriatric Medicine.** Ameri-

(Continued on Page 46)

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GENERAL PRACTITIONERS SPECIALISTS—Are you considering a practice change, please call us, let's talk. We have many opportunities in various West Coast locations. If you would like to join a group, associate or own your own practice we can help. (714) 997-0853, or send CV to physicians Search Associates, 1201 W. La Veta, Suite No. 209, Orange, CA 92668.

SANTA BARBARA COUNTY Department of Health Care Services. Primary Care practice in beautiful North Santa Barbara County. Prefer bilingual English-Spanish ability. Salary negotiable. Contact: Barry Williams, MD, Director, Clinical Services, 300 San Antonio Road, Santa Barbara, CA 93110. Phone (805) 967-2311, Ext. 240.

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DIAGNOSTIC RADIOLOGIST—with minimum 1 year fellowship neuroradiology to perform general diagnosis with neuro emphasis. Group with office and hospital practice, medium size Pacific Northwest city. Salary negotiable. CV to reply Box 6320, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SAN DIEGO, CALIFORNIA. Seeking full-time career oriented Emergency Physician with ED exp; board eligible/cert preferred; 250 bed acute care facility in ideal location. Send CV and refs to Lisa Saarni, MD, Clinical Director Emergency Med Services, Sharp Cabrillo Hospital, 3475 Kenyon St., San Diego, CA 92110. (714) 222-0411.

MEDICAL DIRECTOR OF EMERGENCY UNIT, Presbyterian Hospital—Opportunity for Board Certified/Eligible physician with emergency care skills and interest in medical staff relationships, program development, education, operations, marketing and community relations. Salary/benefits negotiable. Send résumé to George Hunt, Director of Ambulatory Services, Pacific Medical Center, P.O. Box 7999, San Francisco, CA 94120.

MINOR EMERGENCY CLINICS: Full time physician openings for Fair Oaks (Sacramento area) and Vacaville (near Napa Valley) clinics. New modern facilities. Part-time, fill-in positions also available. Malpractice coverage provided. Call Dr. Kendall Bauer (916) 933-1449 evenings.

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CALIFORNIA, SAN JOSE: Experienced Emergency Physician wanted to join established group practicing in Emergency Departments at a University affiliated medical center and a community hospital. Fee-for-service compensation, flexible schedules. Send CV or contact: James B. Lane, MD, 1541 The Alameda, Suite A, San Jose, CA 95126. Phone (408) 293-8881.

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SANTA BARBARA, CALIFORNIA: Primary Care immediate openings in Family Practice or Internal Medicine to join dynamic 65 physician multispecialty clinic with primary care branch offices. Excellent benefit package. Board eligible/certified. Send CV to: Administration, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102.

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(Continued on Page 42)

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FAMILY PRACTITIONER—Board certified, would like to buy active office-hospital practice in West San Fernando Valley. Partnership considered. Write and send particulars to Box 6330, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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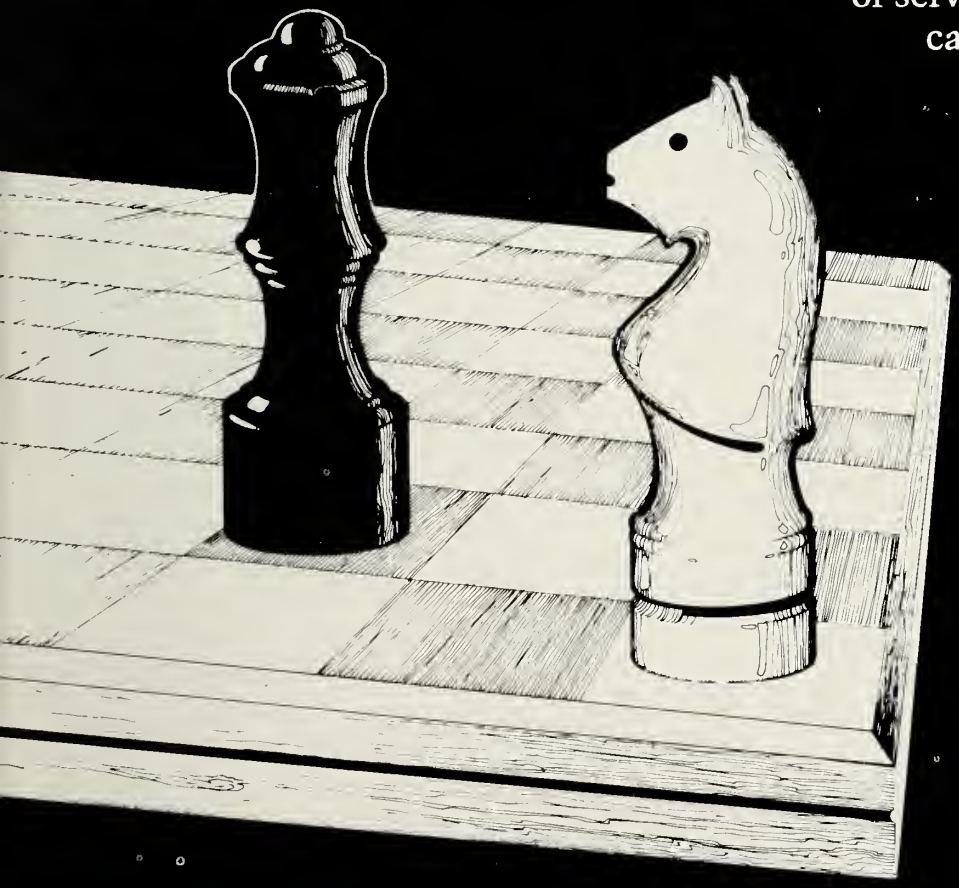

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Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

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Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

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The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers, and month and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Andersen HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978 Apr 26; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978 Sep; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, IL, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, MA, Publishing Sciences Group, Inc, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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(Continued from Page 38)

can College of Physicians at Santa Monica. 9 days. Contact: Registrar, ACP, 4200 Pine St., Philadelphia 19104. (215) 243-1200.

January 17-18—**International Symposium: The Psychobiology of Alcoholism.** UCLA at Beverly Hilton, Beverly Hills. Monday-Tuesday. 13 hrs. $225.

January 21—**Medical Consequences of Nuclear Weapons and Nuclear War.** UCD at Sacramento Convention Center, Sacramento. Friday.

January 22—**Rape and Domestic Violence.** UCLA. Saturday.

January 24-28—**Primary Care: Current Management of Common Office Problems.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Tuesday. 33 hrs. $300.

February 2-4—**Neurology for Non-Neurologists.** UCSD at Hilton, San Diego. Wednesday-Friday. 23 hrs. Contact: Edith S. Bookstein, 7810 Lookout Dr., La Jolla 92037. (619) 454-3212.

February 5—**Alcohol and Drug Problems in the Later Years.** UCLA. Saturday. 5½ hrs. $100.

February 7-11—**Nutritional Aspects of Obesity Management.** American Society of Bariatric Physicians at Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. $295, members; $325, nonmembers. Contact: ASBP, 5200 S. Quebec, Suite 300, Englewood, CO 80111. (303) 779-4833.

February 7-12—**UCI Family Practice Refresher Course.** UCI at Marriott, Newport Beach. Monday-Saturday. 50-56 hrs. $525. Contact: UCI Extension, P.O. Box AZ, Irvine 92714. (714) 833-5414.

February 9-April 13—**Biofeedback Review Course.** UCLA. Wednesday evenings. 30 hrs.

February 10-12—**Practical Cardiology for Family Physicians, 1983.** American College of Cardiology at Eisenhower Medical Center, Rancho Mirage. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

February 11—**Geriatric Medicine, Symposium II—"Special Health Concerns of the Elderly."** Sutter Community Hospitals at Red Lion Motor Inn, Sacramento. Friday. 7 hrs. Contact: Marsha Vacca, Geriatrics Coordinator, Sutter Gen. Hosp., 28 and L Sts., Sacramento 95816. (916) 454-2222, ext. 1233.

February 12-19—**Updates in Acute Medicine: An Epic Medical Expedition.** American Inst. of Primary Care Medicine and Univ. of Arizona College of Medicine at Maui. One week. 24 hrs. Contact: Richard Paris, MD, P.O. Box 209, Sun Valley, ID 83353.

February 14-25—**Intensive Residency in Occupational Medicine, II.** UCSF at Golden Gateway Holiday Inn, San Francisco. Two weeks. 80 hrs.

February 20-25—**Winter Sports Injuries.** UCD at Hyatt, Lake Tahoe. Sunday-Friday. 15 hrs.

February 21-25—**Basic Science for Clinicians.** STAN. Monday-Friday. 25 hrs. $365.

March 3-6—**Critical Care Medicine—21st Annual Symposium.** USC at MGM Grand, Las Vegas. Thursday-Sunday. 28 hrs.

March 5-6; 19-20—**San Francisco Academy of Hypnosis—Annual Workshop.** Letterman Army Medical Center, San Francisco. Two weekends. 28 hrs. $275. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco 94114.

March 5-12—**Future Directions and Update on Family Practice.** Univ. of Washington School of Medicine at Sheraton Royal Waikiloa, Kona. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

March 9-11—**33rd Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Nancy Drungilas, Office of Cont. Ed., Mt. Zion Hosp., P.O. Box 7921, San Francisco 94120. (415) 567-6600, ext. 2404.

March 9-11—**American Society for Clinical Pharmacology and Therapeutics.** Town and Country Hotel, San Diego. Wednesday-Friday. Contact: ASCPT, 1718 Gallagher Rd., Norristown, PA 19401.

March 10-13—**Clinical Management.** STAN at The Lodge, Pebble Beach. Thursday-Sunday. 12 hrs. $250.

March 11-16—**California Medical Association—112th Annual Session.** Bonaventure Hotel, Los Angeles. Friday-Wednesday. Contact: Joan Kammerer, CMA.

March 12—**Total Parenteral Nutrition.** UCLA. Saturday.

March 19-26—**Advances in Drug Therapy.** Univ. of Washington School of Medicine at Royal Lahaina, Maui. One week. Contact: U/W Sch. of Med., Div. of CME, SC-50, Seattle 98195. (206) 543-1050.

March 26—**Alcoholism and Its Treatment: 1983.** UCD at Sacramento Inn, Sacramento. Saturday. 7 hrs.

April 8—**Common Problems in an Aging Population.** LLU at Casa Royale Motor Inn, Bakersfield. Friday. 6 hrs.

April 13—**Antiobiotic Update—1983.** LLU. Wednesday. 4 hrs.

April 14-16—**Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite. Thursday-Saturday. Contact: Charlotte Newhart, CMA.

April 20-24—**Mountain Medicine.** UCD at Stanford Sierra Lodge, Fallen Leaf Lake. Wednesday-Sunday. 22 hrs.

IDAHO

January 15-22—**Updates in Pediatrics: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 19-26—**Updates in Acute Medicine: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

March 19-26—**Updates in Trauma: An Epic Medical Expedition—Alpine Skiing Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Sun Valley. Saturday-Saturday. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

August 15-19—**Pediatric Immunology and Infectious Disease** (Sponsor: University of Utah). Monday-Friday. Sun Valley. 25 hrs. Fee to be announced. Contact: John Matsen, MD, (801) 581-5968.

See also Washington Listings: February 12-19, 14-18, 19-26.

MONTANA

January 8-15—**Updates in Acute Medicine: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Saturday-Saturday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 8-15—**Updates in Trauma: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Tuesday-Tuesday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

February 15-20—**Big Sky/Ski Symposium.** Big Sky. Tuesday-Sunday. Contact: American Lung Association of Montana, 825 Helena Ave., Helena, MT 59601. (406) 442-6556.

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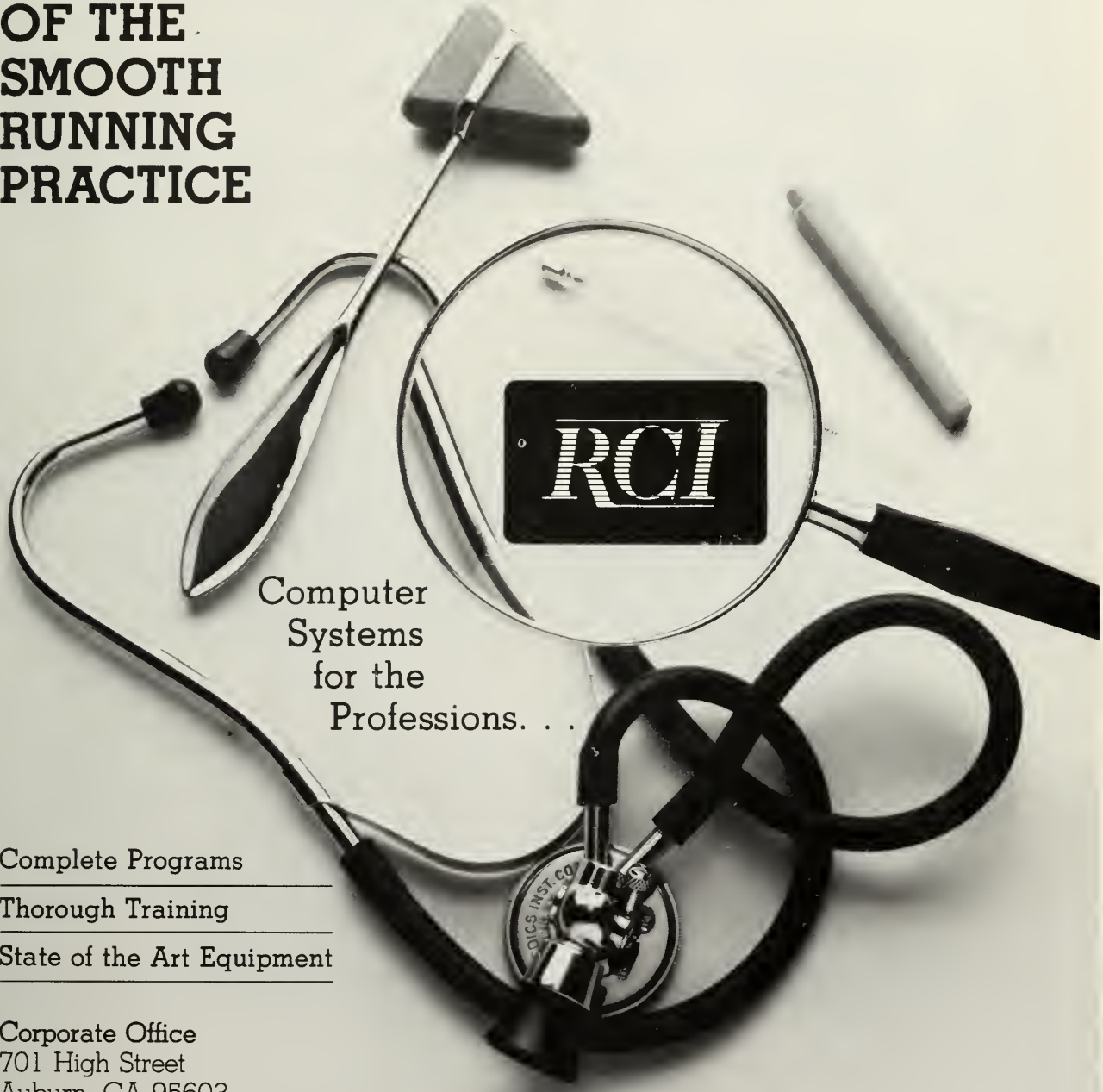

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(Continued from Page 46)

March 26-April 2—**Updates in Pediatrics: An Epic Medical Expedition—Ski Touring Conference** (Sponsors: American Institute of Primary Care Medicine and the University of Arizona College of Medicine). Big Sky. Saturday-Saturday. Lone Mountain Ranch. 24 credit hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353.

NEW MEXICO

All courses listed below have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. The Continuing Medical Education Committee of the New Mexico Medical Society has certified all courses listed below as meeting the criteria for Category IV under the New Mexico Board of Medical Examiners Continuing Medical Education regulations.

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15-16—**Semi-Annual Clinical Meeting: New Mexico Academy of Family Physicians.** Albuquerque. Saturday-Sunday. Marriott Hotel. 12 credit hours, also AAFP Prescribed. Contact: New Mexico Academy of Family Physicians, 303 San Mateo NE, #204, Albuquerque, NM 87108. (505) 266-7868.

January 28-29—**Physicians Conference on Alcoholism & Chemical Dependence.** Albuquerque. Friday-Saturday. Marriott Hotel. 12 credit hours. Contact: Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7621 (Rod Waller, CARE UNIT) or (505) 842-7000 (Martin Conway, MD).

February 14-17—**Taos Medical Symposium.** Taos. Monday-Thursday. Kachina Lodge. 16 credit hours, also AAFP. Contact: Taos Medical Symposium, James A. Schneider II, MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

February 27-March 3—**New Mexico Metabolism Symposium.** Taos. Sunday-Thursday. Tennis Ranch of Taos. 15 credit hours. Contact: Martin Conway, MD, Lovelace Medical Center, 5400 Gibson Blvd. SE, Albuquerque, NM 87108. (505) 842-7000.

February 28-March 4—**Purgatory Ski Symposium.** Durango, Colorado. Monday-Friday. Tamaron Lodge. 20 credit hours, also AAFP. Contact: Gwenn Robinson,MD, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108. (505) 266-7868.

OREGON

The following list of continuing medical education offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to Veronica Story, Secretary to the Council on Medical Education, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein St., Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7111.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, OR 97213. (503) 234-8211.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00-9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee, P.O. Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.**

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

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2801 Atlantic Avenue
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Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr. Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Rd., Portland 97225. (503) 297-4411, Ext. 2230.

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

* * * *

FAMILY PRACTICE

February 14-18—**Annual Family Practice Review.** Portland. Monday-Friday. Red Lion Motor Inn at Lloyd Center. For information contact: OHSU-CME.

EMERGENCY MEDICINE

February 11-12—**Poisonings & Toxicologic Emergencies.** Portland. Friday-Saturday. Red Lion Motor Inn at Lloyd Center. For information contact: Veronica Story, Oregon ACEP, 5210 SW Corbett, Portland, OR 97201. (503) 226-1555.

PATHOLOGY

March 10-11—**Workshop in Dermatopathology.** Portland. Thursday-Friday. Oregon Medical Association, 5210 SW Corbett. For information contact: OHSU-CME.

SURGERY

December 3—**Soft Tissue Surgery Techniques.** Portland. Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

INTEREST TO ALL PHYSICIANS

March 4-5—**Complex and Controversial Issues in Multiple System Trauma.** Portland. Friday-Saturday. Red Lion Inn Downtown. For information contact: OHSU-CME.

March 11-12—**1983 Mid-Willamette Valley Cancer Conference on Lung Cancer.** Gleneden Beach. Friday-Saturday. Salishan Lodge. For information contact: Beverly Kay, Executive Secretary, Salem Hospital, P.O. Box 14001, Salem, OR 97309. (503) 370-5339.

April 13-15—**Sommer Memorial Lectures/Alumni Association Scientific Sessions.** Portland. Wednesday-Friday. Oregon Health Sciences University Campus. For information contact: OHSU-CME.

May 20-21—**Orthopedics for the Primary Care Physician.** Portland. Friday-Saturday. Red Lion Motor Inn-Lincoln St. For information contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the Academy for Continuing Medical Education, a foundation of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Academy for Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the Academy at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the Academy for current details.

PEDIATRIC GRAND ROUNDS

Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103:

First and Third Thursdays—8:00 a.m. Contact: Cathy Van Komen, PCMC, 320 12th Ave., Salt Lake City, UT 84103. (801) 363-1221.

MONTHLY PSYCHOTHERAPY CLINICAL SEMINAR

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

First Monday—7-9 a.m. Contact: Jack Tedrow, MD, (801) 363-2024.

FAMILY PRACTICE CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

(Continued to Page 52)

SPONSORS OF COURSES—ABBREVIATIONS

AF:	Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.
CWH:	Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461
FHP:	Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.
HAFB:	Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.
HCH:	Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.
LDSH:	Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.
OEH:	Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409
PCMC:	Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.
SHCC:	Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.
SLSC:	Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.
UAFP:	Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.
UUMC:	University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.
USMA:	Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.
UVH:	Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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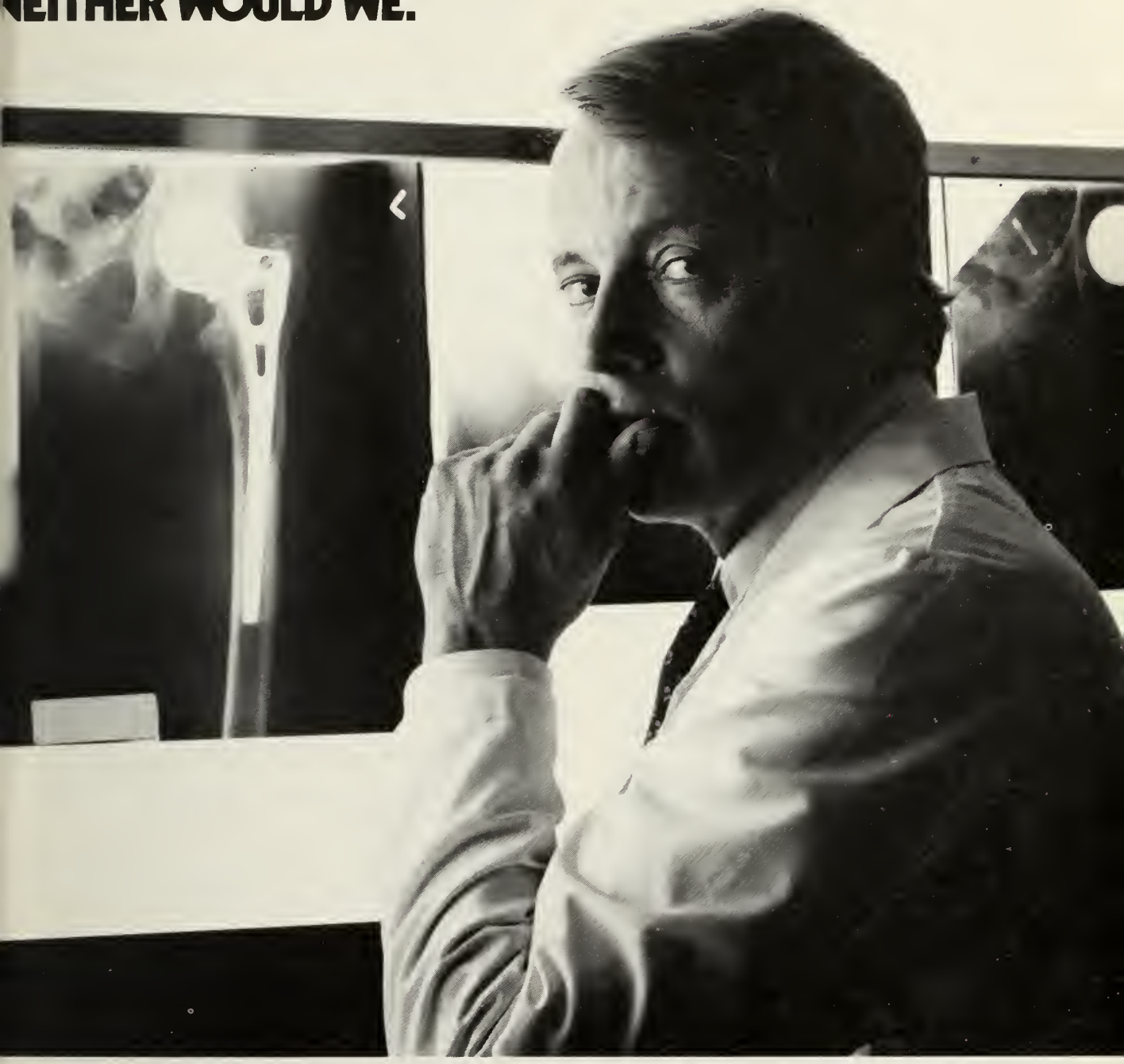

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(Continued from Page 50)

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CITYWIDE OB/GYN CLINICAL CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Second Saturday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

OB/GYN PATHOLOGY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—8-9 a.m. Contact: Howard Berk, MD, (801) 364-4438.

MONTHLY OPHTHALMOLOGY FLUORESCEIN ANGIOGRAPHY CONFERENCE

Holy Cross Hospital, 1045 East First South, Salt Lake City 84102.

Fourth Monday—7:30-8:30 a.m. Contact: Roy Goodart, MD, (801) 532-7406 or F. T. Reikhof, MD, (801) 532-7406.

INTERDEPARTMENTAL GRAND ROUNDS

Utah Valley Hospital, Provo, 1034 North Fifth West, Provo 84601.

Contact: Gary Watts, MD, UVH, 1034 North Fifth West, Provo, UT 84601. (801) 373-7850 (Ext 2143).

* * * *

January 7—**Effect of Surgery for Variceal Hemorrhage on Hepatic Blood Flow and Cerebral Function/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

January 21—**Treatment of Upper Extremity Pain Syndromes** (Sponsor: McKay-Dee Hospital Center). Ogden. Friday. 1 hr. No fee. Contact: (801) 627-3202.

January 21-23—**7th Annual U of U Seminar on Sexual Function/Dysfunction** (Sponsor: University of Utah). Park City. Friday-Sunday. 19 hrs. Fee: $200. Contact: Claire Turner (801) 581-5809.

January 26-February 3—**Air Transport Workshop** (Sponsor: University of Utah). Salt Lake City. Wednesday-Thursday. Credit and fee to be announced. Contact: Dennis C. Brimhall, MD (801) 581-2682.

January 31-February 4—**Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Park City. Monday-Friday. 25 hrs. $350. Contact: John Matsen, MD (801) 581-5514.

February 4—**Host Functions Essential for Bacteriophage Growth/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

February 14-17—**12th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. Salt Lake Hilton. 28 hrs. $280. Contact: Linda Twitchell (801) 581-8633.

February 18-22—**28th Annual Postgraduate Course in Anesthesiology** (Sponsor: University of Utah). Salt Lake City. Friday-Tuesday. Hilton Hotel. 17 hrs. Fee to be announced. Contact: Ted Stanley, MD (801) 581-7647.

February 19-22—**24th Annual Ob/GYN Postgrad Course** (Sponsor: University of Utah). Park City. Saturday-Tuesday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 23-26—**Perinatal Update** (Sponsor: University of Utah). Park City. Wednesday-Saturday. 15 hrs. $275. Contact: David Engleberg (801) 581-7647.

February 25—**Special Problems in Stroke Recovery** (Sponsor: McKay-Dee Hospital Center). Ogden. Thursday. 1 hr. No fee. Contact: (801) 627-3202.

February 26-27—**Head, Neck/Spine CT** (Sponsor: University of Utah). Salt Lake City. Saturday-Sunday. Little America Hotel. 11 hrs. Fee to be announced. Contact: Robert Anderson, MD (801) 581-8188.

March 2-4—**Intermountain Pediatric Society/Common Problems in Pediatrics** (Sponsor: University of Utah). Salt Lake City. Wednesday-Friday. 15 hrs. $200. Contact: Richard O'Brien, MD (801) 363-1221/#250.

March 4—**Blood and Marrow Neutrophil Kinetics During Group B Streptococcal Sepsis/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

March 5-6—**Digital Angiography/Interventional Medicine** (Sponsor: University of Utah). Salt Lake City. Saturday-Sunday. Little America Hotel. 12.5 hrs. Fee to be announced. Contact: Franklin Miller, MD (801) 581-8188.

March 7-11—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Snowbird. Monday-Friday. 22.5 hrs. $275. Contact: Jennifer Fossum (801) 581-3581.

March 10-11—**Rocky Mountain Infection Control Association/Infection Control Update** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Little America Hotel. 12 hrs. $85-$100. Contact: Sego Matsumiya, RN (801) 582-1565.

March 11—**Forensic Pathology Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. Skaggs Hall, University Medical Center. 7 hrs. $85. Contact: Wallace Graham, MD (801) 533-5848.

March 14-19—**Basic Science Update/Practicing MD's: Impact of Modern Biology on Medical Practice** (Sponsor: University of Utah). Park City. Monday-Friday. Yarrow. 25 hrs. $300. Contact: Donald F. Summers, MD (801) 581-8664.

March 18-19—**Advanced Trauma Life Support** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. Salt Lake Hilton Inn. 14.5 hrs. $375. Contact: Kim Tanner, RN (801) 533-6608.

March 21-25—**3rd Annual Nutrition in Contemporary Medicine Conference** (Sponsor: University of Utah). Park City. Monday-Friday. 29 hrs. $225. Contact: Jennifer Fossum (801) 581-3581.

March 24-25—**Ethical, Legal and Religious Concerns in Reproductive Medicine** (Sponsor: University of Utah). Salt Lake City. Thursday-Friday. University of Utah Campus. 15 hrs. $70. Contact: Robert Fineman, MD (801) 581-8943.

April 1—**Connective Tissue Genes: Their Structure and Expression in Cells of the Arterial Wall/Interdepartmental Research Seminar** (Sponsor: University of Utah). Salt Lake City. Friday. School of Medicine. 1 hr. No fee. Contact: Rosalie Lammle (801) 581-8664.

April 5-8—**The 5th Annual RMCOEH Occupational and Environmental Health Conference: Reproduction: The New Frontier in Occupational and Environmental Health Research** (Sponsor: University of Utah/RMCOEH). Park City. Tuesday-Friday. Prospector Square. Credit and fee to be announced. Contact: Ms. K. Blosch (801) 581-5710.

June 1-3—**Computers in Critical Care and Pulmonary Medicine** (Sponsor: University of Utah). Salt Lake City. Wednesday-Friday. Hotel Utah. 12 hrs. $250. Contact: Vicky Larsen (801) 581-6393.

June 20-33—**Alcoholism and Other Drug Dependencies** (Sponsor: University of Utah). Salt Lake City. Monday-Thursday. University of Utah Campus. 25 hrs. Fee to be announced. Contact: James Swenson, MD (801) 581-7985.

July 11-15—**Diagnostic Microbiology and Immunology** (Sponsor: University of Utah). Jackson Hole, Wyoming. Monday-Friday. 25 hrs. Fee to be announced. Contact: John Matsen, MD (801) 581-5968.

August 15-19—**Pediatric Immunology and Infectious Disease** (Sponsor: University of Utah). Monday-Friday. Sun Valley, Idaho. 25 hrs. Fee to be announced. Contact: John Matsen, MD (801) 581-5968.

Note: Dates, times, places and programs are subject to change on occasion. Please check with the sponsoring organization or the Academy for details.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the course sponsors and contact information box.

January 6-7—**Special Topics in Sexuality.** Seattle. Thursday-Friday. Westin Hotel. Contact: U/W.

January 15—**Hepatobiliary Disease for the Primary Physician: Clinical Aspects and Imaging Choices.** Seattle. Saturday. Providence Medical Center. Contact: Evelyn Foote, Providence Medical Center, 500 17th Ave, C-34008, Seattle, WA 98124. (206) 326-5821.

January 21-22—**Ophthalmic Plastic and Reconstructive Surgery.** Seattle. Friday-Saturday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 23—**Dyslexia.** Seattle. Sunday. Sheraton Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Academy of Ophthalmology, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

January 27-28—**Current Therapy in Cardiology.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

February 4-5—**Diseases of the Elderly.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

February 5-12—**(OREGON) Advanced Cardiac Life Support.** Sunriver. Saturday-Saturday. Sunriver Resort. Contact: U/W.

February 12-19—**(IDAHO) Office Orthopaedics.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 14-18—**(IDAHO) Sun Valley Primary Care Conference.** Sun Valley. Monday-Friday. Sun Valley Lodge. Contact: Marilyn R. Carlson, Continuing Education, Northwest Hospital, 1551 North 115th, Seattle, WA 98133. (206) 364-0500, ext. 1737.

February 19-26—**(IDAHO) Infectious Diseases.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 24-25—**Contemporary Clinical Neurology.** Seattle. Thursday-Friday. Virginia Mason Medical Center. Contact: VMMC.

February 26-March 5—**(HAWAII) Management of Pain.** Kauai. Saturday-Saturday. Kauai Surf. Contact: U/W.

March 4-5—**High-Risk Infants of the 1980s.** Seattle. Wednesday-Friday. Children's Orthopedic Hospital. Contact: U/W.

March 5-12—**(HAWAII) Future Directions and Update on Family Practice.** Kona. Saturday-Saturday. Sheraton Royal Waikiloa. Contact: U/W.

March 11-12—**Nutrition and Bone Metabolism.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

March 12-19—**(HAWAII) Office Gynecology, Ophthalmology, Otolaryngology, Urinary and Breast Disease.** Kona. Saturday-Saturday. Sheraton Royal Waikoloa. Contact: U/W.

March 16-18—**MKSAP: Medical Knowledge Self-Assessment Program.** Seattle. Wednesday-Friday Virginia Mason Medical Center. Contact: VMMC.

March 18—**Endocrine Day.** Seattle. Friday. U/W CDMRC. Contact: U/W.

March 18-19—**Sex Offenders.** Seattle. Friday-Saturday. U/W South Campus Center. Contact: U/W.

March 18-19—**Recent Developments in Occupational Medicine.** Seattle. Friday-Saturday. U/W Health Sciences Building. Contact: U/W.

March 19-26—**(HAWAII) Advances in Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 25-26—**Advanced Cardiac Life Support.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

March 26—**Pathology Day.** Seattle. Saturday. U/W Health Sciences Building. Contact: U/W.

March 26-April 2—**(HAWAII) Vascular Disease.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 1-2—**Compensation Law/Public Policy/Back Pain.** Seattle. Thursday-Friday. Sheraton Hotel. Contact: U/W.

April 2—**Anesthesia Care Team Meeting.** Seattle. Saturday. Westin Hotel. Contact: Marcia Wahlman, Executive Secretary, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle, WA 98121. (206) 623-4801.

April 11-22—**Rehabilitation Medicine Review.** Seattle. Sunday-Thursday. Sheraton. Contact: U/W.

April 28-29—**Financial Planning for Physicians.** Seattle. Wednesday-Thursday. Sheraton Hotel. Contact: U/W.

May 5-6—**Health Issues for Exercising Women.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

May 6—**Primary Care Urology.** Seattle. Friday. Virginia Mason Medical Center. Contact: VMMC.

May 13-14—**Hypertension.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

May 19-20—**Diabetes.** Seattle. Thursday-Friday. U/W Health Sciences Building. Contact: U/W.

May 20-21—**Prescription and Nonprescription Drugs.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

June 3—**Endocrine Day.** Seattle. Friday. CDMRC. Contact: U/W.

June 3-4—**Acute Medical Problems.** Seattle. Friday-Saturday. Virginia Mason Medical Center. Contact: VMMC.

June 9-11—**Common Office Procedures.** Seattle. Wednesday-Friday. U/W Health Sciences Building. Contact: U/W.

June 23-24—**Nosocomial Infections Herpes Hepatitis.** Seattle. Thursday-Friday. U/W South Campus Center. Contact: U/W.

June 26-July 1—**(OREGON) Office Management of Common Psychiatry Problems.** Sunriver. Sunday-Friday. Sunriver Resort. Contact: U/W.

July 1-4—**(OREGON) Scientific Aspects of Dance.** Ashland. Friday-Monday. Southern Oregon College. Contact: U/W.

July 6-9—**(OREGON) Ethical and Legal Aspects of Medical Practice.** Gleneden. Wednesday-Saturday. Salishan Resort. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs. Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON) — Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Sandra McDonald, Division of Continuing Medical Education, Virginia Mason Medical Center, 1100 Ninth Avenue, P.O. Box 900, Seattle, WA 98101. (206) 223-6898.

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 277-6891. Annual Meeting: May 28-31, 1983, Cordova.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: May 19-21, 1983, Doubletree Inn, Tucson.

California Medical Association—731 Market St., San Francisco 94103. (415) 777-2000. Annual Meeting: March 11-16, 1983, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. (303) 861-1221. Annual Meeting: 1983—date and place to be announced.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1983—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 20-23, 1983, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1983—date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 12-15, 1983, Elko Convention Center, Elko.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 4-6, 1983. Four Seasons Motor Hotel, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Scientific Session: 1983—date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1983—date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: 1983—date and place to be announced.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Winter Seminar: January 21-22, 1983, Rawlins; Annual Meeting: June 29-July 2, 1983, Jackson Lake Lodge, Moran.

July 10-15—**(OREGON) Medicine and Society in History.** Sunriver. Sunday-Friday. Sunriver Resort. Contact: U/W.

July 21-22—**American College of Physicians MKSAP VI.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

July 28—**Wound Healing.** Seattle. Wednesday. Westin Hotel. Contact: U/W.

July 28-30—**Debates in Otolaryngology.** Seattle. Wednesday-Friday. Westin Hotel. Contact: U/W.

July 29-30—**Trauma and Burns.** Seattle. Wednesday-Thursday. Westin Hotel. Contact: U/W.

July 29-31—**Washington State Society of Anesthesiologists: Seafair V Anesthesia Meeting.** Seattle. Sheraton. Contact: Washington State Society of Anesthesiology, Marcia Wahlman, Executive Secretary, 2033 Sixth Avenue, Suite 900, Seattle, WA 98212. (206) 623-4801.

August 4-5—**Sports Medicine Summer 1983.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

August 4-6—**Pharmacotherapy and Psychotherapy.** Seattle. Thursday-Saturday. U/W Health Sciences Building. Contact: U/W.

August 18-19—**Advances in Behavioral Medicine.** Seattle. Wednesday-Friday. U/W Health Sciences Building. Contact: U/W.

August 25-26—**Urology for Urologists.** Seattle. Wednesday-Thursday. U/W Health Sciences Building. Contact: U/W.

WYOMING

January 21-22—**Wyoming Medical Society Winter Seminar.** Rawlins. Friday-Saturday. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

June 29-July 2—**Wyoming Medical Society Annual Meeting.** Moran. Wednesday-Saturday. Jackson Lake Lodge. For information contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne, WY 82003-4009.

July 11-15—**Diagnostic Microbiology and Immunology** (Sponsor: University of Utah). Jackson Hole. Monday-Friday. 25 hrs. Fee to be announced. Contact: John Matsen, MD (801) 581-5968.

Index to
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AYERST LABORATORIES
Inderide 32, 33, 34
BANK OF AMERICA 3
BANKERS INVESTMENT CO., THE 35
BOYLE & COMPANY/PHARMACEUTICALS
Citra Forte Syrup—Citra Forte Capsules 14
BURROUGHS WELLCOME CO.
Zyloprim 45
CALIFORNIA MEDICAL ASSOCIATION
112th Annual Session 16
CLASSIFIED 40, 42
COOPERATIVE OF AMERICAN PHYSICIANS
Mutual Protection Trust 48
CPS MEDICAL BILLING SYSTEMS 41
DOCTORS' CO., THE 51
ELI LILLY & CO.
Ceclor 36
GENERAL ARABIAN MEDICAL AND ALLIED SERVICES LTD. 39
MERCK SHARP & DOHME
Heptavax-B 19, 20, 21, 22, 23
NORCAL MUTUAL INSURANCE CORPORATION 10
PERALTA HOSPITAL—EDUCATION DEPARTMENT
Cancer Update—1983 35
PFIZER
Procardia 24, 25, 26, 27, 28, 29, 30
PHYSICIANS & SURGEONS INSURANCE EXCHANGE 12
PRACTICE SERVICE CORPORATION 43
RCI COMPUTER SERVICES 47
RESEARCH INDUSTRIES INC.
Rimso-50—Rimso-100 31
RHEUMATOLOGY DIAGNOSTIC LABORATORIES INC. 6
ROCHE LABORATORIES
Medical Education 17, 18
Dalmane ..... 2nd cover, 1, 2
Valium ..... 3rd and 4th covers
SMITH KLINE & FRENCH LABORATORIES
Dyazide 4
UNIVERSITY OF CALIFORNIA, IRVINE
DEPT. OF RADIOLOGICAL SCIENCES
Radiology of the Emergency Patient 2
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Frontiers in Radiology 49
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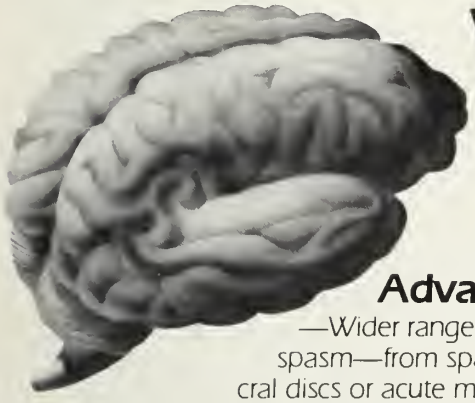
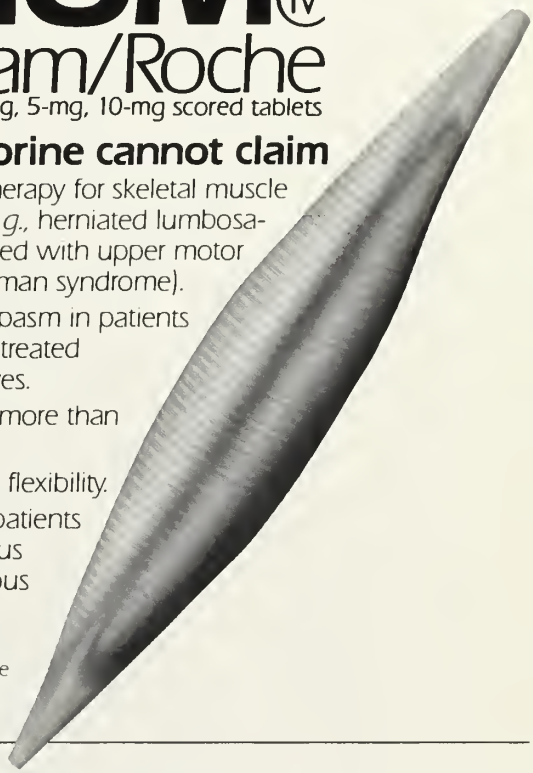
THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



Adjunctive
VALIUM® (IV)
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets



Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.*, herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.*, cerebral palsy, athetosis, stiff-man syndrome).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA: *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome; convulsive disorders (not for sole therapy)
The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
The clearance of Valium (diazepam/Roche) and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

How Supplied: For oral administration, Valium (diazepam/Roche) scored tablets—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100* and 500.* Prescription Paks of 50, available in trays of 10.* Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25,† and in boxes containing 10 strips of 10.†

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BACK AGAIN

the spasm/pain/spasm cycle

Skeletal muscle spasm tends to recur—usually because predisposing factors (such as muscle weakness, faulty posture and obesity) remain uncorrected, so that even minor trauma may set off painful spasm.[1,2] The key to therapeutic relief is to stop the spasm. In some patients with skeletal muscle spasm who also experience excessive anxiety, Valium® (diazepam/Roche) provides a unique dual advantage— it is indicated for the management of anxiety disorders and also adjunctively for the relief of muscle spasm due to local pathology.

For skeletal muscle spasm due to local pathology

Adjunctive

VALIUM®(IV)

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2-mg, 5-mg, 10-mg scored tablets

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